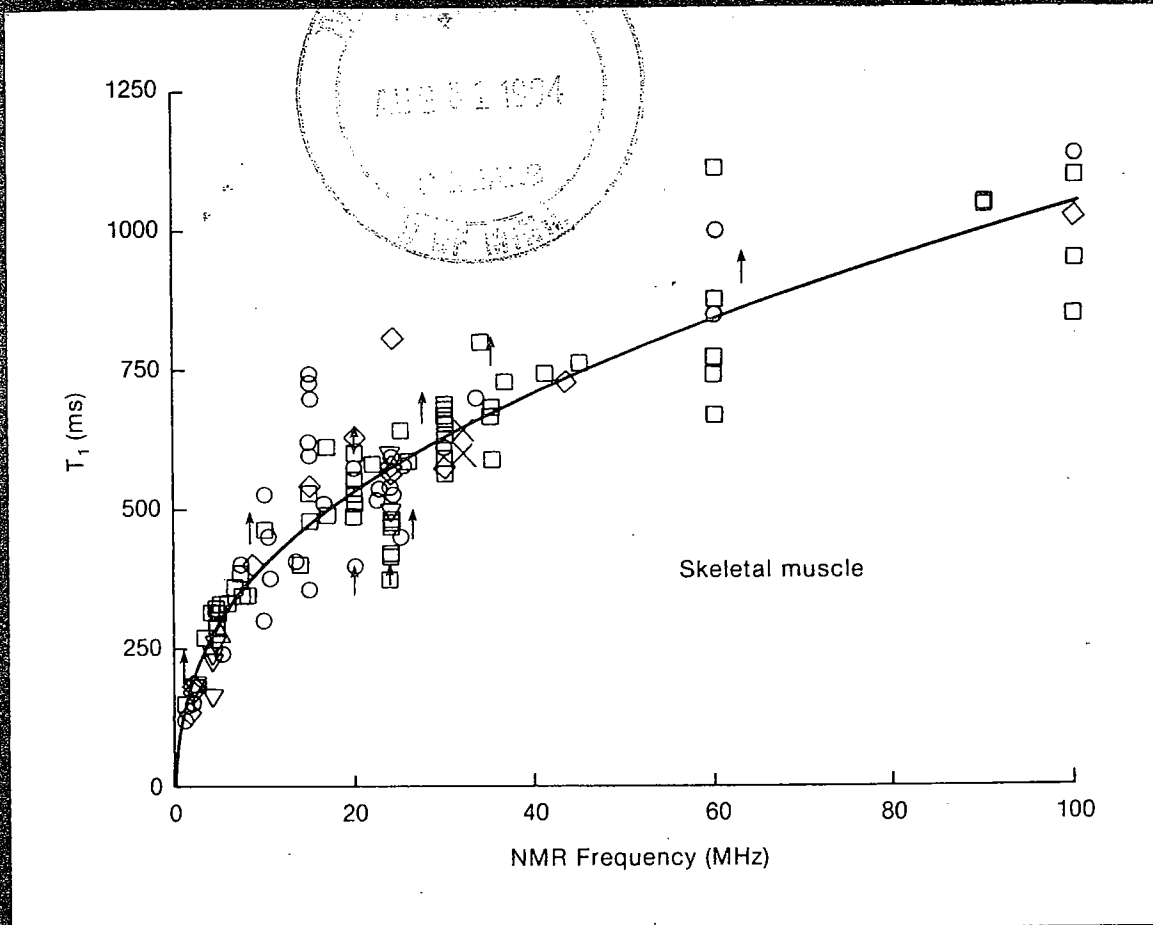


# Exhibit 12

# Medical Physics

July/August 1984

Volume 11, Number 4



**NMR Relaxation Times**

# Medical Physics

Volume 11, Number 4, July/August 1984

## Our Cover

Understanding factors affecting NMR relaxation times is critical to designing and interpreting data from clinical imaging and spectroscopic instrumentation. Our front cover is taken from an article in this issue by Bottomley *et al.* which reviews and analyzes data for normal tissue hydrogen.

## REVIEW ARTICLE

**A review of normal tissue hydrogen NMR relaxation times and relaxation mechanisms from 1–100 MHz: Dependence on tissue type, NMR frequency, temperature, species, excision, and age**

Paul A. Bottomley, Thomas H. Foster, Raymond E. Argersinger, and Leah M. Pfeifer

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**Performance characteristics of A150 plastic-equivalent gases in A150 plastic proportional counters for 14.8-MeV neutrons**

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## REVIEW ARTICLE

# A review of normal tissue hydrogen NMR relaxation times and relaxation mechanisms from 1–100 MHz: Dependence on tissue type, NMR frequency, temperature, species, excision, and age

Paul A. Bottomley, Thomas H. Foster, Raymond E. Argersinger, and Leah M. Pfeifer

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The longitudinal ( $T_1$ ) and transverse ( $T_2$ ) hydrogen ( $^1\text{H}$ ) nuclear magnetic resonance (NMR) relaxation times of normal human and animal tissue in the frequency range 1–100 MHz are compiled and reviewed as a function of tissue type, NMR frequency, temperature, species, *in vivo* versus *in vitro* status, time after excision, and age. The dominant observed factors affecting  $T_1$  are tissue type and NMR frequency ( $\nu$ ). All tissue frequency dispersions can be fitted to the simple expression  $T_1 = A\nu^B$  in the range 1–100 MHz, with  $A$  and  $B$  tissue-dependent constants. This equation provides as good or better fit to the data as previous more complex formulas.  $T_2$  is found to be multicomponent, essentially independent of NMR frequency, and dependent mainly on tissue type. Mean and raw values of  $T_1$  and  $T_2$  for each tissue are tabulated and/or plotted versus frequency and the fitting parameters  $A$ ,  $B$  and the standard deviations determined to establish the normal range of relaxation times applicable to NMR imaging. The mechanisms for tissue NMR relaxation are reviewed with reference to the fast exchange two state (FETS) model of water in biological systems, and an overview of the dynamic state of water and macromolecular hydrogen compatible with the frequency, temperature, and multicomponent data is postulated. This suggests that  $^1\text{H}$  tissue  $T_1$  is determined predominantly by intermolecular (possibly rotational) interactions between macromolecules and a single bound hydration layer, and the  $T_2$  is governed mainly by exchange diffusion of water between the bound layer and a free water phase. Deficiencies in measurement techniques are identified as major sources of data irreproducibility.

Key words: NMR relaxation,  $T_1$ ,  $T_2$ , review, biological tissue, NMR imaging, relaxation mechanisms

## I. INTRODUCTION

Longitudinal ( $T_1$ ) and transverse ( $T_2$ ) nuclear magnetic resonance (NMR) relaxation times play a pivotal role in the understanding of molecular level organization of biological systems in general and in NMR imaging in particular. Differences amongst hydrogen ( $^1\text{H}$ ) NMR relaxation times of normal and pathological tissue are key to NMR image contrast and the discrimination of disease,<sup>1–161</sup> a fact responsible for their widespread use as diagnostic parameters in clinical NMR imaging. They directly effect the selection of imaging pulse sequence timing parameters,<sup>51</sup> and consequently, the total image scan times and patient throughput. They also influence the choice of the optimum magnetic field strength for NMR imaging because of their significant variation with NMR frequency.<sup>22,55,73</sup>

Since the early  $^1\text{H}$  relaxation time studies on animal and human tissue by Odelblad *et al.* in the late 1950s,<sup>89,120–124</sup> the observation of elevated  $T_1$ 's in cancer by Damadian in 1971,<sup>40</sup> and the more general  $T_1$  variations in pathologies reported by Eggleston *et al.* in 1975,<sup>52</sup> the literature has burgeoned with hundreds of investigations of relaxation time

behavior in biological tissue. The majority of publications that report tissue relaxation time measurements ignore or make few attempts to interpret the physical mechanisms responsible for tissue relaxation or to compare them with similar published data, although the issues of species, frequency, temperature, and *in vivo/in vitro* dependence offer mitigating reasons. Moreover, efforts to collate this vast body of relaxation time information for the purpose of establishing the range of normal values and their frequency dependence are nonexistent.

This article reviews the published  $^1\text{H}$  relaxation time data from normal human and animal tissues in an attempt to establish the normal range of  $T_1$  and  $T_2$  values for NMR imaging and their dependence on tissue type, NMR frequency, species, temperature, time after excision, *in vitro* versus *in vivo* measurement, and age. The data are presented graphically, to illustrate trends and deficiencies with the work to date; in tabular form, for locating sources, providing additional information, and for future collation; and as parameters of best fit to a simple expression, to enable rapid computation of the  $T_1$  at any desired frequency. Since



whole-body  $^1\text{H}$  NMR imaging systems currently operate within the frequency range of 1 to 65 MHz, with even higher frequencies imminent.<sup>22,23</sup> data extending over the frequency range 1–100 MHz are examined. Experimental results are analyzed theoretically in terms of available fast exchange two state (FETS) models involving water in essentially free and bound phases in biological tissues, thereby providing a cogent description of the spectrum of  $^1\text{H}$   $T_1$  and  $T_2$  relaxation mechanisms and molecular motions. A similar study of pathological tissue relaxation time data is underway.<sup>24</sup>

## II. METHODS

A current awareness subscription from the New England Research Application Center was conducted from 1980 to 1983 to monitor the abstracting service data bases AGRICOLA (agricultural literature), Biological Abstracts, the Conference Papers Index, Energy Abstracts, the Engineering Index, Index Medicus, INSPEC (physics, electronics and computer abstracts), NTIS (government technical reports), SPIN (physics information), and the US Government Patent File. The search was keyed to tissue NMR relaxation time measurements, NMR imaging, and authors publishing in these research domains. Publications on tissue relaxation times prior to 1980 were searched by cross referencing personal files of papers collected since 1975, in addition to papers cited in the abstracting subscription. This procedure netted about 300 relevant articles by December 1983. One-half of these were rejected either because they contained no explicit relaxation time data for normal tissue; or because the NMR frequency (or field strength) was not stated; or because the relaxation times pertained only to isolated cell cultures, blood serum, plasma, dehydrated or homogenized tissues; or because measurements were performed below 0 °C; or because measurements were taken from tumor or pathology bearing animals; or because  $T_2$  values were calculated from resonance linewidths. Of the remainder, results were presented in the text or in tables or in graphs. Where graphical information was the sole source, relaxation time information was read from the curves directly, thereby introducing some reading error. Arithmetic means are assumed for data tabulated as ranges. Data recorded *in vivo*, from fetal or immature tissue, or under other special circumstances are noted. Finally, data were checked for duplication in publications by the same authors, and in reviews.

## III. RESULTS

### A. Tissue, species, and frequency dependence

$^1\text{H}$  NMR  $T_1$  and  $T_2$  data from normal liver, muscle (skeletal and heart), kidney, spleen, brain (grey and white matter), adipose, breast, lung, body fluids (blood, marrow, cerebral spinal fluid, amniotic fluid, bile, urine) and other miscellaneous tissues are presented in Tables 2–11, respectively. Table 1 summarizes the abbreviations used and the symbol legend for the plotted data. The mean cited standard deviation for each relaxation data point, expressed as a percentage of the  $T_1$  and  $T_2$  values, is about  $(10 \pm 10)\%$  for all tissues.  $T_1$  relaxation is typically characterized by a single-component exponential on a timescale  $> 5$  ms except in several reports of

*in vivo* and *in vitro* measurements of mouse liver and embalmed human liver and muscle,<sup>5</sup> *in vivo* newt tails,<sup>141</sup> *in vitro* rat muscle,<sup>35</sup> and *in vitro* human breast tissue<sup>25,101,113</sup> where dual, relatively long ( $> 50$  ms)  $T_1$  components of comparable magnitude were measured.

The  $T_1$  frequency dispersions of tissues with sufficient data are plotted in Figs. 1–8. Where papers present data recorded at several temperatures, only those closest to physiological values are depicted. Fetal and immature tissue data are excluded from the plots because of their vastly elevated values. Different symbols denote human, rat, mouse, chicken, cow, pig, dog, gerbil, hamster, rabbit, frog, and newt contributions. Skeletal and heart muscle (Fig. 2), and grey and white brain matter (Fig. 5) have different  $T_1$ 's and, therefore, are differentiated where possible. Similarly, kidney cortex and medulla have significantly different  $T_1$ 's, but because few authors make such distinction, segregation of the kidney plot is impractical. Thus Fig. 3 should be regarded cautiously, as an organ average only. Note that for a given tissue type, there is no detectable difference in correlation between  $T_1$  points and NMR frequency due to differences in species (Fig. 1–9), despite individual observations of  $T_1$  differences amongst species by some researchers (Tables 2–11).

Curves of the form

$$T_1 = A\nu^B, \quad (1)$$

where  $A$  and  $B$  are constants and  $\nu$  is the NMR frequency, are fitted to liver, muscle, kidney, spleen, brain, adipose, and lung  $T_1$  dispersions combining all species, using the method of minimizing the sum of the squares of the fractional difference of  $T_1$  data from the curve. Conventional fitting routines that minimize the sum of the squares of the absolute differences between the curve and the data preferentially weight the less numerous high-frequency points. This generates curves that appear better, but have slightly higher fractional errors. Power series expansions, and the dipolar expression for  $T_1$  with a single correlation time (see Sec. IV A) diverge or are less successful at fitting data at extreme frequencies. However, the Escanye *et al.* relation<sup>54</sup>

$$T_1^{-1} = A'\nu^{-1/2} + B', \quad (2)$$

( $A'$ ,  $B'$ , constants) yields quite comparable results. A best fit to the Escanye *et al.* expression is plotted in Figs. 1 and 4 for comparison. Values of the fitting coefficients and the percentage standard deviations (assuming random distributions) of  $T_1$  values from the curves for each tissue are tabulated in Table 12. The curves are not weighted with the number of samples averaged for each point because the scatter in  $T_1$  values measured at the same frequency often greatly exceeds the cited standard deviations. The concentration of disagreeable data around 15 and 20 MHz attests to this. For breast tissue (Fig. 7), where the scatter exceeds 400%, curves from muscle and adipose plots [Figs. 2(a) and 6] are superimposed on the data suggesting tissue heterogeneity as the main cause: breast tissue is apparently a mixture of fibrous and fatty components. The applicability of the curve-fitting algorithm to individual  $T_1$  dispersion data is demonstrated in Fig. 9 with measurements from Escanye *et al.*,<sup>54</sup> and Koenig *et al.*<sup>99</sup>

Tabulated tissue  $T_2$  values appear essentially independent

Table 1.

## KEY TO SYMBOLS USED IN THE TABLES 2-11 AND FIGURES 1-10.

A = Auricle	P = Pregnant
B = Breast	Pa = Parenchyma
C = Cortex	R = Red muscle
Cl = Clotted	Ref = Reference
de = Day embryo	RT = Room temperature
Di = Dead intact	S = Solid component
do = Day old	Sh = Short component
F = Fetus	SL = Semi liquid component
Freq = Frequency	SS = Semi solid component
Hp = Heparinised	T = Temperature at which measurements were made
I = Immature	V = Vivo
Intc = Intercostal	Ven = Ventricle
L = Liquid component	Verte = Vertebral
Lac = Lactating	Vgn = Virgin
Lo = Long component	W = White muscle
M = Medium component	— = Not reported
Med = Medulla	% = Percent of total proton population contribution to this component
N = Number of samples	

Species:

⊙ — rat	— newt (Figure 1) or cow (Figure 5)
× — chicken	+ — hamster
△ — dog	↑ — frog
□ — mouse	↓ — pig
★ — gerbil	▽ — rabbit
◇ — human	

## Units:

$T_1$  and  $T_2$  are in ms, frequencies are in MHz, and temperatures are in degrees °C.

## Note:

In Table 8 the 17, 65 and 75 which precede Lo and Sh indicate the percentage of tissue fat in the breast sample.

of frequency. Figure 10 illustrates the  $T_2$  dispersion for liver.  $T_2$  data scatter is significantly greater than for  $T_1$ . Many researchers report multiple ( $\leq 4$ )  $T_2$  components that constitute between 6% and 76% of the total observed tissue NMR signal intensity (Tables 2-11). Only the single  $T_2$  component values are used in Fig. 10 and in computing the average  $T_2$  values listed in Table 12.

### B. Temperature dependence

The vast majority of tabulated relaxation data were measured either at room temperature ( $\sim 23^\circ\text{C}$ ) for *in vitro* studies, or physiological temperature ( $\sim 37^\circ\text{C}$ ) for *in vivo* measurements. The effect of temperature on  $T_1$  was noted by Frey *et al.*<sup>59</sup> and Damadian *et al.*<sup>42</sup> The former reported that mice spleen  $T_1$  depends "only mildly" on temperature from 5-40 °C, whereas the latter commented that "temperature

control was found to be important" in the precise determination of  $T_1$ 's. Neither group presented data supporting these assertions.

Quantitative investigations were undertaken by Barroilhet and Moran,<sup>5</sup> Escanye *et al.*,<sup>54,55</sup> Finch and Homer,<sup>57</sup> Fung,<sup>62</sup> Fung and McGaughy,<sup>64</sup> Fung *et al.*,<sup>63</sup> Parker *et al.*,<sup>125</sup> Koenig *et al.*,<sup>99</sup> and Lewa and Majewska.<sup>102</sup> Barroilhet and Moran concluded that "in general, relaxation times are strongly temperature dependent," although the principal effect of a temperature increase was an elevation in the longer of the dual  $T_1$  components observed in embalmed human tissue, whereas the initial slope average  $T_1$  in two samples increased less than 7% between 20 and 33 °C. Escanye *et al.* recorded mice  $T_1$ 's of muscle, spleen, liver, and kidney at 20 (Ref. 54) and 24 °C<sup>55</sup> and at NMR frequencies between 10 and 90 MHz without significant difference. Over

Table 2. Liver

T1	T2	Freq	N	T	Species	Ref	T1	T2	Freq	N	T	Species	Ref
100	-	1.0	1	35	dog	99	281	32	20.0	16	-	rat	137
120	-	1.0	1	35	rabbit	99	320	-	20.0	1	30	rat	99
84	-	1.0	1	-	rat	85	250	40	20.0	54	23	rat	46
107	-	1.0	1	30	rat	99	205	63	20.0	6	40	rat	72
123	-	1.6	1	30	rat	99	271	38	22.5	5	-	rat	68
155	-	1.7	20	V	human	90,147,148,149,150	339	-	24.0	-	-	human	109
105	-	2.0	1	-	rat	85	350	-	24.0	10	26	mouse	12,39
133	-	2.0	1	30	rat	99	283	-	24.0	1	RT	mouse	84
141	-	2.5	3	20	rabbit	105	296	-	24.0	1	RT	mouse	84
138	36	2.7	10	19	mouse	38	271	-	24.0	10	RT	mouse	84
133	-	3.0	1	35	dog	99	263	-	24.0	1	RT	mouse	12,84
182	-	3.0	1	35	rabbit	99	400	-	24.0	-	-	rabbit	109
154	-	3.0	1	30	rat	99	311	-	24.0	3	23	rabbit	105
194	-	4.3	-	V	rabbit	70	309	-	24.0	-	-	rabbit	109
215	37	4.3	-	V	rabbit	70,71	324	-	24.0	-	-	rat	109
210	-	4.5	-	37	mouse	63	309	-	24.0	12	25	rat	50
190	-	4.5	-	28	mouse	63	296	-	24.0	72	-	rat	106
186	49	5.0	50	RT	rat	156	293	52	24.0	5	-	rat	12,40
153	-	5.0	1	-	rat	85	301	-	24.3	1	26	dog	39
200	-	5.0	1	30	rat	99	303	-	24.3	5	26	hamster	39
161	44	5.1	6	-	dog	160,161	383	-	24.3	8	26	human	39
160	-	5.1	6	25	rabbit	160	280	-	24.3	10	23	mouse	142
250	-	6.5	10	-V	human	129	225	-	24.3	4	23	mouse	86
240	-	6.5	12	V	human	49,154	-	51	24.3	2	26	mouse	39
392	-	6.7	-	20	mouse	54	353	-	24.3	4	26	rabbit	39
229	-	7.0	1	30	rat	99	205	-	24.3	32	23	rat	86
250	-	7.5	-	37	mouse	63	270	-	24.3	-	24	rat	87
215	-	7.5	-	28	mouse	63	721	-	25.0	1	23	human(F)	94
240	-	8.0	1	20	mouse	5	375	-	25.0	6	25	mouse	144
228	-	8.0	10	V	mouse	5	370	-	25.0	-	20	mouse	54
251	-	8.0	11	-	mouse(Di)	5	426	-	25.0	26	25	mouse	144
165	-	8.0	2	-	rat	58	274	-	25.0	1	-	rat	85
172	-	8.0	3	-	rat	58	438	-	25.3	27	-	mouse	134
163	-	8.0	2	-	rat	58	273	-	25.3	3	RT	rat	12,37
153	-	8.0	2	-	rat	58	-	53	25.6	5	33	hamster	103
380	40	8.5	10	V	human	139	-	48	25.6	5	33	hamster	103
171	-	10.0	1	35	dog	99	-	68	25.6	5	33	hamster	103
275	-	10.0	-	20	mouse	54	298	-	30.0	4	-	human	92
275	-	10.0	20	24	mouse	55	385	-	30.0	-	20	mouse	54
267	-	10.0	1	35	rabbit	99	341	-	30.0	25	-	mouse	92
205	-	10.0	1	-	rat	85	400	-	30.0	20	24	mouse	55
232	-	10.0	1	30	rat	99	386	-	30.0	7	25	mouse	59
225	-	10.7	2	RT	rat	33	361	-	30.0	2	-	mouse	92
235	-	10.7	4	-	rat	18	382	-	30.0	1	25	mouse	59
-	47	10.7	8	-	rat	18	356	-	30.0	1	30	rat	99
300	-	12.0	-	37	mouse	63	-	47	30.0	-	-	rat	34
275	-	12.0	-	28	mouse	63	412	33	30.3	6	25	mouse	12,76
238	-	13.6	4	-	rat	17	438	33	30.3	6	25	mouse	12,76
-	49	15.0	11	V	human	158	208	-	32.0	6	25	chicken	12,136
293	37	15.0	10	19	mouse	38	475	-	35.0	-	37	mouse	63
-	25	15.0	1	25	mouse	59	425	-	35.0	-	28	mouse	63
-	30	15.0	1	25	mouse	59	410	-	36.5	-	20	mouse	54
315	-	15.0	-	20	mouse	54	-	78	60.0	1	22	human(Lo)	146
267	-	15.0	1	30	rat	99	-	12	60.0	1	22	human(Sh)	146
418	37	15.0	16	V	rat	152	520	-	60.0	20	24	mouse	55
520	40	15.0	-	V	rat	43,44,80	531	-	60.0	11	27	mouse	4
420	38	15.0	8	V	rat	43,44,80	630	-	60.0	-	37	mouse	63
222	-	15.0	1	-	rat	85	560	-	60.0	-	28	mouse	63
396	-	17.1	-	25	mouse	108	467	-	60.0	4	25	rat	12,26
285	-	17.1	-	25	rat	108	580	33	60.0	2	RT	rat	95
182	-	20.0	1	35	dog	99	340	30	60.0	2	20	rat	96,97
397	96	20.0	3	40	human	72	527	43	60.0	2	20	rat(I)	96,97
350	-	20.0	-	20	mouse	54	640	-	90.0	20	24	mouse	55
375	-	20.0	20	24	mouse	55	635	-	90.0	-	20	mouse	54
411	-	20.0	20	RT	mouse	112	570	-	100.0	14	26	human	12,41,42
325	-	20.0	-	37	mouse	63	420	37	100.0	-	-	mouse	12,91
300	-	20.0	-	28	mouse	63	550	30	100.0	5	-	mouse	91
280	-	20.0	-	22	newt	141	637	-	100.0	4	-	rat	17
182	41	20.0	8	40	pig	72	612	-	100.0	4	-	rat	18
356	-	20.0	1	35	rabbit	99							

Table 3. Muscle

T1	T2	Freq	N	T	Species	Ref	T1	T2	Freq	N	T	Species	Ref
(a.) Skeletal Muscle													
230	56	1.0	-	25	frog	78	538	55	24.0	5	-	rat	12,40
118	-	1.0	1	-	rat	85	596	-	24.0	18	25	rat	107
151	-	1.1	-	25	mouse	62	807	-	24.3	2	26	human	39
130	-	1.7	-	V	human	150	475	-	24.3	4	23	mouse	142
180	-	1.7	-	V	human	90	465	-	24.3	4	23	mouse	86
130	-	1.7	-	V	human	148	525	-	24.3	-	24	rat	87
184	-	1.7	1	V	rabbit	104	641	-	25.0	-	20	mouse	54
163	-	1.7	1	-	rabbit(Di)	104	449	-	25.0	1	-	rat	85
150	-	2.0	1	-	rat	85	-	195	25.0	-	24	rat(Lo,10%)	75
175	-	2.3	-	25	mouse	62	-	45	25.0	-	24	rat(M,82%)	75
182	-	2.5	3	20	rabbit	105	-	5	25.0	-	24	rat(Sh,8%)	75
183	-	2.5	3	20	rabbit(Abd)	105	575	-	25.6	10	25	rat,cow	102
191	-	2.5	3	20	rabbit(Intc)	105	588	-	26.0	-	25	mouse	98
181	42	2.5	36	20	rat	104	490	46	26.5	-	14	frog	57
185	49	2.7	10	19	mouse	38	700	44	27.5	-	23	frog	57
270	-	3.5	-	25	mouse	62	574	-	30.0	7	-	human	92
290	64	4.0	-	25	frog	78	635	-	30.0	1	25	mouse	59
312	-	4.0	-	25	mouse	62	563	-	30.0	3	-	mouse	92
250	40	4.3	-	-	frog	28	660	-	30.0	20	24	mouse	55
241	-	4.3	-	V	rabbit	70	590	-	30.0	25	-	mouse	92
264	-	4.3	-	V	rabbit	70	690	-	30.0	-	20	mouse	54
-	21	4.3	-	V	rabbit	70	680	-	30.0	-	25	mouse	61
259	28	4.3	-	V	rabbit	70,71	615	-	30.0	8	25	mouse	59
165	-	4.3	-	-	rabbit	70	625	-	30.0	-	25	mouse	62
225	-	4.3	-	-	rabbit(Di)	70	637	-	30.0	-	25	mouse	98
323	-	4.5	-	37	mouse	62	586	-	30.0	4	-	mouse(P)	92
294	-	4.5	-	28	mouse	62	608	-	30.0	-	25	rat	8
310	-	4.5	2	30	rat	64	642	-	32.0	6	25	chicken(R)	136
-	65	5.0	-	25	frog	78	598	-	32.0	6	25	chicken(W)	136
310	-	5.0	-	25	mouse	61	700	-	33.5	2	30	rat	64
333	-	5.0	-	25	mouse	62	800	60	33.8	-	21	mouse	140
240	-	5.0	1	-	rat	85	-	143	33.8	-	20	mouse(L,7%)	128
270	64	5.1	5	25	dog	160,161	-	2	33.8	-	20	mouse(S,11%)	128
245	-	5.1	6	25	rabbit	160	-	41	33.8	-	20	mouse(SL,76%)	128
333	-	6.0	-	25	mouse	62	-	503	33.8	-	20	mouse(SS,6%)	128
360	-	6.7	-	20	mouse	54	800	58	35.0	-	25	frog	78
420	63	7.0	-	25	frog	78	684	-	35.0	-	25	mouse	98
385	-	7.5	-	37	mouse	62	667	-	35.0	-	37	mouse	62
345	-	7.5	-	28	mouse	62	589	-	35.0	-	28	mouse	62
400	-	7.5	2	30	rat	64	730	-	36.5	-	20	mouse	54
345	-	8.0	-	25	mouse	62	741	-	41.0	-	25	mouse	98
480	64	8.5	-	25	frog	78	725	-	43.5	5	37	human	21
400	50	8.6	10	V	human	139	762	-	45.0	-	25	mouse	98
460	-	10.0	20	24	mouse	55	-	168	60.0	30	20	frog(Lo,15%)	14
461	-	10.0	-	20	mouse	54	-	38	60.0	30	20	frog(M,67%)	14
525	-	10.0	10	-	rat	130	-	10	60.0	30	20	frog(Sh,18%)	14
301	-	10.0	1	-	rat	85	740	-	60.0	11	27	mouse	4
450	-	10.5	2	30	rat	64	875	-	60.0	20	24	mouse	55
376	-	10.7	2	RT	rat	33	667	-	60.0	-	25	mouse	62
404	-	13.6	4	-	rat	17	1111	-	60.0	-	37	mouse	62
400	-	14.0	-	25	mouse	62	769	-	60.0	-	28	mouse	62
541	35	15.0	13	V	human	116	1000	-	60.0	2	-	rat	64
476	51	15.0	10	20	mouse	38	850	-	60.0	6	25	rat	12,26
-	36	15.0	2	25	mouse	59	950	63	63.0	-	25	frog	78
529	-	15.0	-	20	mouse	54	1053	-	90.0	-	20	mouse	54
744	30	15.0	5	V	rat	115	1050	-	90.0	20	24	mouse	55
356	33	15.0	3	V	rat	81	1023	-	100.0	17	26	human	11,12,41,42
620	29	15.0	11	V	rat	81	1100	-	100.0	-	25	mouse	61
596	33	15.0	11	V	rat	81	950	45	100.0	5	-	mouse	91
355	-	15.0	1	-	rat	85	850	57	100.0	5	20	mouse	12,91
725	32	15.0	21	V	rat	44	1138	-	100.0	4	-	rat	17
700	28	15.0	5	V	rat	45	(b.) Heart Muscle						
510	-	16.5	2	30	rat	64	187	-	1.0	1	30	rat	99
488	-	17.0	-	25	mouse	98	250	-	1.7	-	V	human	90,148
610	-	17.1	-	25	mouse	108	295	-	2.5	3	20	rabbit(A)	105
1246	-	20.0	5	36	chicken(1do)	114	243	-	2.5	3	20	rabbit(Ven)	105
746	-	20.0	5	36	chicken(8do)	114	333	70	5.1	6	25	dog	160,161
647	-	20.0	5	36	chicken(16do)	114	263	-	5.1	6	25	rabbit	160
1234	-	20.0	5	36	chicken(18do)	114	434	-	10.7	2	RT	rat	33
1244	-	20.0	5	36	chicken(20do)	114	650	42	15.0	6	-	dog	82
390	47	20.0	-	14	frog	57	-	35	15.0	1	25	mouse	59
650	63	20.0	-	25	frog	78	-	45	15.0	1	25	mouse	59
629	45	20.0	3	40	human	72	630	-	17.1	-	25	mouse	108
528	-	20.0	20	RT	mouse	112	644	75	20.0	3	40	human	72
523	-	20.0	20	RT	mouse	112	576	-	20.0	20	-	mouse	112
500	-	20.0	-	25	mouse	62	688	71	20.0	8	40	pig	72
599	-	20.0	-	20	mouse	54	654	70	20.0	6	40	rat	72
600	-	20.0	20	24	mouse	55	590	43	20.0	-	37	rat(Lo)	20
556	-	20.0	-	37	mouse	62	-	13	20.0	-	37	rat(Sh)	20
488	-	20.0	-	28	mouse	62	480	-	23.3	6	23	mouse	142
605	58	20.0	8	40	pig	72	486	-	24.0	1	RT	mouse	84
400	-	20.0	1	-	rat	85	490	-	24.0	1	RT	mouse	84
576	61	20.0	6	40	rat	72	476	-	24.0	1	RT	mouse	84
581	-	22.0	-	25	mouse	98	706	-	24.0	3	23	rabbit(A)	105,109
517	50	22.5	5	-	rat	68	637	-	24.0	3	23	rabbit(Ven)	105
536	51	22.5	5	-	rat	68	700	-	24.0	-	-	rabbit(Ven)	109
400	40	24.0	-	-	frog	28	481	-	24.0	-	25	rat	50
575	-	24.0	5	-	human	109	873	-	24.3	5	26	human	39
415	-	24.0	1	RT	mouse	84	550	-	24.3	-	24	rat	87
372	-	24.0	1	RT	mouse	84	518	-	25.3	3	RT	rat	37
411	-	24.0	10	RT	mouse	84	620	-	25.6	10	25	rat,cow	102
471	-	24.0	1	RT	mouse	12,84	664	-	30.0	1	25	mouse	59
554	-	24.0	3	23	rabbit	105	650	-	30.0	7	25	mouse	59
500	-	24.0	-	-	rabbit	109	936	69	60.0	2	20	mouse(I)	96,97
534	-	24.0	3	23	rabbit(Abd)	105	873	46	60.0	3	20	rat	96,97
600	-	24.0	-	-	rabbit(Abd)	109	906	-	100.0	9	26	human	41,42
519	-	24.0	3	23	rabbit(Intc)	105							
600	-	24.0	-	-	rabbit(Intc)	109							



Table 4. Kidney

T1	T2	Freq	N	T	Species	Ref
160	-	1.0	1	30	rat	99
320	-	1.7	20	V	human	90,147,148,150,151
200	-	2.0	1	30	rat	99
206	-	2.5	3	20	rabbit (C)	105
426	-	2.5	3	20	rabbit (Med)	105
214	56	2.7	10	19	mouse	38
229	-	3.0	1	30	rat	99
335	-	4.3	-	-	rabbit	70
-	70	4.3	-	V	rabbit	70,71
419	-	4.3	-	V	rabbit	70,71
359	-	4.3	-	V	rabbit	70
419	39	4.3	-	V	rabbit	70
230	-	4.3	-	V	rabbit (C)	70
433	-	4.3	-	-	rabbit (Di)	70
520	-	4.3	-	V	rabbit (Med)	70
320	-	5.0	1	30	rat	99
312	69	5.1	6	-	dog (C)	161
604	171	5.1	6	-	dog (Med)	161
216	-	5.1	6	25	rabbit (C)	160
473	-	5.1	6	25	rabbit (Med)	160
319	-	6.7	-	20	mouse	54
360	-	7.0	1	30	rat	99
670	50	8.5	10	V	human	139
370	-	10.0	-	20	mouse	54
260	-	10.0	20	24	mouse	55
400	-	10.0	1	30	rat	99
342	-	10.7	2	RT	rat	33
410	-	13.6	-	-	rat	17
670	57	15.0	-	V	human (C)	88
516	-	15.0	23	V	human (Pa)	53
-	35	15.0	1	25	mouse	59
415	-	15.0	-	20	mouse	54
390	59	15.0	10	19	mouse	38
-	42	15.0	1	25	mouse	59
467	-	15.0	1	30	rat	99
671	52	15.0	1	V	rat (Pa)	27
524	-	17.1	-	25	mouse	108
634	-	17.1	-	25	rat	108
765	124	20.0	3	40	human	72
450	-	20.0	20	24	mouse	55
391	-	20.0	20	RT	mouse	112
455	-	20.0	-	20	mouse	54
405	96	20.0	8	40	pig	72
533	-	20.0	1	30	rat	99
510	81	20.0	6	40	rat	72
459	-	24.0	-	25	human	12,84
370	-	24.0	1	RT	mouse	84
314	-	24.0	1	RT	mouse	84
290	-	24.0	-	25	mouse	50
286	-	24.0	1	RT	mouse	84
294	-	24.0	10	RT	mouse	84
500	-	24.0	-	-	rabbit	109
406	-	24.0	3	23	rabbit (C)	105
801	-	24.0	3	23	rabbit (Med)	105
480	-	24.0	5	-	rat	40
450	-	24.0	3	-	rat	106
534	-	24.3	1	26	dog	39
398	-	24.3	4	26	hamster	39
770	-	24.3	4	26	human	39
396	-	24.3	10	26	mouse	39
330	-	24.3	10	23	mouse	142
-	52	24.3	2	26	mouse	39
322	-	24.3	4	23	mouse	86
363	-	24.3	2	26	rabbit	39
390	-	24.3	-	24	rat	87
365	-	24.3	32	23	rat	86
993	-	25.0	1	23	human (F)	94
581	-	25.0	6	25	mouse	144
612	-	25.0	15	25	mouse	144
490	-	25.0	-	20	mouse	54
577	-	25.3	3	RT	rat	37
520	-	30.0	1	25	mouse	59
526	-	30.0	-	20	mouse	54
449	-	30.0	3	-	mouse	92
520	-	30.0	20	24	mouse	55
452	-	30.0	25	-	mouse	92
470	-	30.0	9	25	mouse	59
-	61	30.0	-	-	rat	34
503	47	30.3	6	25	mouse	12,13,76
551	50	30.3	6	25	mouse	12,76
403	-	32.0	6	25	chicken	136
602	45	33.8	-	21	mouse	140
565	-	36.5	-	20	mouse	54
800	-	45.0	1	30	rat	99
577	-	60.0	11	27	mouse	4
700	-	60.0	20	24	mouse	55
760	27	60.0	2	RT	rat	95
685	56	60.0	2	20	rat	96,97
668	-	60.0	12	25	rat	26
860	-	90.0	20	24	mouse	55
870	-	90.0	-	20	mouse	54
862	-	100.0	13	26	human	41,42
903	-	100.0	-	-	rat	17

a wider temperature range of 4 to 25 °C, Finch and Homer reported increases in frog muscle  $T_1$  from 0.4 to 0.53 s measured at 23.3 MHz: the dependence was linear with reciprocal of absolute temperature ( $1/T$ ). Fung and colleagues studied mouse muscle and liver  $T_1$ 's from 0.01 to 100 MHz over a temperature range of about -70 to 40 °C: increases in  $T_1$  (linear in  $1/T$ ) of approximately 20%, 30%, and 40% between 17 and 37 °C at 7.5, 35, and 60 MHz were measured, respectively. Parker *et al.* observed an essentially linear increase in blood  $T_1$  between 0 and 50 °C with the increase between 20 and 37 °C being about 30% at 15 MHz. The  $T_1$  values also varied linearly with  $1/T$ . Similarly, Koenig *et al.* measured  $T_1$  increases of 23% at 1 MHz to 85% at 20 MHz as a result of increasing the temperature of rabbit blood from 5 to 35 °C. Lewa and Majewska presented a comprehensive study of rat and cow liver, muscle, heart, spleen, and lung tissue  $T_1$ 's over a 10 to 70 °C temperature range at 15.6 MHz. Their data (Fig. 11) indicate  $T_1$  increases of about 10% between room and physiological temperatures, also linear in  $1/T$ .

Few investigations of the temperature dependence of tissue  $T_2$ 's above freezing point were found. Finch and Homer<sup>57</sup> reported no change in frog muscle  $T_2$  between 4 and 25 °C at 23.3 MHz, within experimental error. Belton *et al.*<sup>14</sup> reported a decrease in frog muscle  $T_2$ 's with increasing temperature from 0 to 25 °C. The widespread observation of multiple  $T_2$  components and large  $T_2$  scatter (Fig. 10) renders dubious the value of analyzing the tabulated  $T_2$  data for temperature dependence.

### C. Time after excision

Tabulated *in vitro* data were recorded up to 12 h following excision or death. Therefore the dependence of tissue relaxation on time after excision is another potential source of variation amongst *in vitro* data. It has been extensively studied.<sup>5,8,35,37,39-42,45,59,68,84,99,126,127,141,156</sup>

Frey *et al.*<sup>59</sup> and Hollis *et al.*<sup>84</sup> noted no appreciable change in mouse and human tissue  $T_1$ 's kept at room temperature in air-tight tubes 12 to 24 h after excision. Damadian<sup>40</sup> measured decreases in  $T_1$  of less than 10% from human liver, kidney, and brain. Cottam *et al.*<sup>39</sup> also measured  $T_1$  changes of less than 10% in mouse liver, spleen, kidney, lymph node, and lymph sarcoma tissues kept at room temperature for 24 h. Damadian measured more marked decreases of 36% and 11% for human stomach and small intestine. Pearson *et al.*<sup>127</sup> observed no significant change in porcine muscle  $T_1$  and in the dominant (short)  $T_2$  component at 1.75 and 24 h postmortem. Similarly, Thickman *et al.*<sup>156</sup> reported constant  $T_1$ 's of untreated rat liver and spleen tissue kept at room temperature for 6 h after excision, and declines in  $T_1$  of only 12% and 18% in liver and spleen, respectively, after 24 h. They observed essentially no change in the  $T_2$  of both rat liver and spleen samples over 48 h following excision. In apparent contrast, Small *et al.*<sup>145</sup> reported dual component  $T_2$  measurements of human breast tissue which "decline significantly as a function of time" when stored at room temperature. Examination of the data, however, indicates

Table 5. Spleen

T1	T2	Freq	N	T	Species	Ref	T1	T2	Freq	N	T	Species	Ref
240	-	1.0	1	35	rabbit	99	366	-	24.0	9	RT	mouse	84
219	-	1.0	1	30	rat	99	458	-	24.0	1	RT	mouse	84
150	-	1.0	1	-	rat	85	529	-	24.0	-	-	rabbit	109
240	-	1.5	1	30	rat	99	509	-	24.0	3	23	rabbit	105, 109
270	-	1.7	20	V	human	90, 148, 149, 150	505	-	24.0	72	-	rat	106
125	-	2.0	-	-	mouse	48	531	-	24.0	-	-	rat	109
246	-	2.0	1	30	rat	99	539	-	24.3	1	26	dog	39
192	-	2.0	1	-	rat	85	600	-	24.3	1	26	hamster	39
258	-	2.5	3	20	rabbit	105	567	-	24.3	1	23	human	67
263	66	2.7	10	19	mouse	38	519	-	24.3	1	23	human	67
320	-	3.0	1	35	rabbit	99	680	-	24.3	10	26	human	39
291	-	3.0	1	30	rat	99	425	-	24.3	5	23	mouse	142
261	63	5.0	50	RT	rat	156	-	61	24.3	2	26	mouse	39
400	-	5.0	1	30	rat	99	571	-	24.3	9	26	mouse	39
344	107	5.1	6	30	dog	161	614	-	24.3	3	26	rabbit	39
333	-	5.1	6	25	rabbit	160	510	-	24.3	-	24	rat	87
510	-	6.5	-	V	human	49, 129, 154	658	-	25.0	20	25	human	144
405	-	6.7	-	20	mouse	54	712	-	25.0	14	25	mouse	144
457	-	7.0	1	30	rat	99	637	-	25.0	-	20	mouse	54
287	-	8.0	2	-	rat	58	406	-	25.0	1	-	rat	85
273	-	8.0	4	-	rat	58	457	-	25.3	3	RT	rat	37
278	-	8.0	2	-	rat	58	-	72	25.6	5	33	hamster	103
420	20	8.5	-	V	human	139	-	78	25.6	5	33	hamster	103
480	-	10.0	20	24	mouse	55	-	69	25.6	5	33	hamster	103
481	-	10.0	-	20	mouse	54	580	-	25.6	10	25	rat, cow	102
533	-	10.0	1	35	rabbit	99	521	-	26.0	-	25	mouse	98
533	-	10.0	1	30	rat	99	500	-	30.0	-	-	mouse	48
306	-	10.0	1	-	rat	85	523	-	30.0	21	-	mouse	92
443	-	10.7	2	RT	rat	33	571	45	30.0	9	25	mouse	59
-	-	15.0	11	V	human	158	563	35	30.0	1	25	mouse	59
-	-	15.0	1	25	mouse	59	541	-	30.0	-	25	mouse	98
-	-	15.0	1	25	mouse	59	676	-	30.0	-	20	mouse	54
493	70	15.0	10	19	mouse	38	680	-	30.0	20	24	mouse	55
549	-	15.0	-	20	mouse	54	582	-	30.0	12	25	rat	26
426	-	17.0	-	25	mouse	98	671	45	30.3	6	25	mouse	76
641	-	17.1	-	25	mouse	108	737	55	30.3	6	25	mouse	76
461	-	17.1	-	25	rat	108	596	-	32.0	6	25	chicken	12, 136
760	140	20.0	3	40	human	72	-	33	33.7	10	23	mouse	47
566	-	20.0	101	RT	mouse	112	700	40	33.8	21	21	mouse	140
606	-	20.0	-	20	mouse	54	578	-	35.0	-	25	mouse	98
600	-	20.0	20	24	mouse	55	752	-	36.5	-	20	mouse	54
507	64	20.0	8	40	pig	72	625	-	41.0	-	25	mouse	98
800	-	20.0	1	35	rabbit	99	645	-	45.0	-	25	mouse	98
385	-	20.0	1	-	rat	85	800	-	45.0	1	30	rat	99
800	-	20.0	1	30	rat	99	762	-	60.0	6	27	mouse	4
431	94	20.0	6	40	rat	72	840	-	60.0	20	24	mouse	55
500	-	22.0	-	25	mouse	98	980	-	90.0	-	20	mouse	54
535	-	24.0	-	-	human	109	950	-	90.0	20	24	mouse	55
433	-	24.0	1	RT	mouse	84	701	-	100.0	17	26	human	11, 12, 41, 42
399	-	24.0	1	RT	mouse	84	-	-	-	-	-	-	-

Table 6. Brain

T1	T2	Freq	N	T	Species	Tissue	Ref	T1	T2	Freq	N	T	Species	Tissue	Ref
255	-	1.7	-	V	human	cerebellum	147	474	-	13.7	4	-	rat	-	17
275	-	1.7	-	V	human	grey-cerebrum	147	847	56	15.0	5	V	gerbil	cerebrum-l.hem	110
303	-	1.7	22	V	human	grey-frontal	16	809	54	15.0	5	V	gerbil	cerebrum-r.hem	110
299	-	1.7	22	V	human	grey-occipital	16	-	45	15.0	6	25	mouse	-	59
304	-	1.7	22	V	human	grey-parietal	16	488	78	15.0	9	19	mouse	-	38
287	-	1.7	-	V	human	grey-matter	148	880	57	15.0	6	V	rat	-	44
262	-	1.7	-	V	human	grey-matter	90	640	-	17.1	-	25	rat	-	108
255	-	1.7	-	V	human	spinal.cord	147	630	98	20.0	3	40	human	grey-matter	72
255	-	1.7	-	V	human	spinal.cord	90	825	110	20.0	4	37	human	white-matter	119
225	-	1.7	-	V	human	white-cerebrum	147	687	107	20.0	4	37	human	homogenized	112
244	-	1.7	22	V	human	white-frontal	16	584	-	20.0	20	RT	mouse	-	72
250	-	1.7	22	V	human	white-occipital	16	713	102	20.0	8	40	pig	cerebel.cortex	72
248	-	1.7	22	V	human	white-parietal	16	816	122	20.0	8	40	pig	grey-cerebrum	72
232	-	1.7	-	V	human	white-matter	90	850	104	20.0	8	40	pig	pons	72
237	-	1.7	-	V	human	white-matter	148	516	112	20.0	8	40	pig	spinal.cord	72
410	-	1.7	-	V	human(I)	grey-matter	148	676	87	20.0	8	40	pig	white-cerebrum	72
410	-	1.7	-	V	human(I)	white-matter	148	589	70	20.0	6	40	rat	-	72
273	-	1.8	27	V	human	cerebel.cortex	65	483	-	24.0	10	RT	mouse	-	84
248	-	1.8	27	V	human	cerebel.medul	65	517	-	24.0	3	RT	mouse	-	84
288	-	1.8	27	V	human	grey-frontal	65	570	-	24.0	3	23	rabbit	cerebellum	105
250	-	1.8	27	V	human	pontine.region	65	700	-	24.0	-	-	-	cerebellum	109
227	-	1.8	27	V	human	white-frontal	65	644	-	24.0	3	23	rabbit	grey-matter	105
326	-	2.5	3	23	rabbit	cerebellum	105	644	-	24.0	3	23	rabbit	grey-matter	105
308	-	2.5	3	23	rabbit	med.oblongata	105	700	-	24.0	-	-	-	med.oblongata	105,109
325	-	2.5	3	23	rabbit	spinal.cord	105	493	-	24.0	3	23	rabbit	spinal.cord	105
285	75	2.7	9	19	mouse	-	38	464	-	24.0	3	23	rabbit	white-matter	105
410	-	5.0	3	25	mouse	homogenized	61	469	-	24.0	5	-	rat	-	40
290	100	5.1	2	-	dog	brain.stem	161	595	-	24.0	-	24	mouse	-	87
429	115	5.1	3	-	dog	cerebellum	161	590	-	24.3	-	23	mouse	cerebrum	142
427	118	5.1	13	-	dog	grey-matter	161	795	-	24.3	5	23	mouse	-	37
345	114	5.1	3	-	dog	pituitary	161	472	-	25.3	3	RT	rat	-	59
350	98	5.1	2	-	dog	thalamus	161	693	-	30.0	1	25	mouse	-	59
262	133	5.1	11	-	dog	white-matter	161	646	-	30.0	6	25	mouse	homogenized	61
399	-	6.3	1	V	human	-	29	800	-	30.0	3	25	mouse	grey-matter	93
515	-	6.5	10	V	human	grey-caudate.nuc	32	660	-	32.0	10	RT	rat	white-matter	93
525	-	6.5	10	V	human	grey-crbll.cortex	32	560	-	32.0	10	RT	rat	grey-matter	126
540	-	6.5	10	V	human	grey-inslr.cortex	32	-	88	60.0	15	32	dog	grey-matter	126
430	-	6.5	10	V	human	grey-lentic.nuc.	32	435	105	60.0	10	32	human	grey-matter	126
375	-	6.5	10	V	human	grey-thalamus	32	-	65	60.0	7	32	human	white-matter	126
-	110	6.5	6	V	human	grey-matter	3	1361	149	60.0	2	20	mouse(I)	-	96,97
295	-	6.5	10	V	human	white-frogs.mjr	32	866	71	60.0	3	20	rat	-	96,97
285	-	6.5	10	V	human	white-frogs.mnr	32	998	-	100.0	8	26	human	-	41,42
-	105	6.5	6	V	human	white-matter	3	880	-	100.0	-	20	mouse	-	91
311	80	10.7	-	RT	bovine	white-matter	66	840	88	100.0	5	20	mouse	homogenized	12,91,96
405	-	10.7	2	RT	rat	-	33	1030	-	100.0	3	25	mouse	-	61
585	90	12.8	4	V	human	cerebellum	157	1174	-	100.0	4	-	rat	-	17
710	100	12.8	4	V	human	cerebrum	157	1146	76	100.0	5	25	rat	grey-matter	118
600	115	12.8	4	V	human	cerebrum	157	1078	76	100.0	5	25	rat	white-matter	118
490	90	12.8	4	V	human	cerebrum	157	1280	57	150.0	18	-	gerbil	-	30,31
600	100	12.8	4	V	human	cerebrum(ave)	157	1830	-	150.0	6	-	gerbil(1do)	-	30
380	80	12.8	4	V	human	corpus.callosum	157	1330	-	150.0	2	-	gerbil(21do)	-	30
600	100	12.8	2	V	human	grey-matter	157	1260	-	150.0	6	-	gerbil(21do)	-	30
475	100	12.8	4	V	human	medulla	157	1820	-	150.0	5	-	gerbil(2do)	-	30
445	75	12.8	4	V	human	pons	157	1780	-	150.0	4	-	gerbil(8do)	-	30
380	80	12.8	2	V	human	white-matter	157	-	-	-	-	-	-	-	-

Table 7. Adipose

T1	T2	Freq	N	T	Species	Ref
171	-	1.5	1	30	rat	99
130	-	1.7	-	V	human	90
145	-	1.7	28	V	human	148
70	-	1.7	40	V	human	150
146	-	1.8	3	V	human(B)	138
175	-	2.0	1	30	rat	99
187	-	3.0	1	30	rat	99
75	-	4.3	-	-	rabbit	70
183	-	4.3	-	V	rabbit	70, 71
196	-	4.3	-	V	rabbit	70
-	63	4.3	-	V	rabbit	70
-	69	4.3	-	V	rabbit	70, 71
172	-	4.3	-	V	rabbit	70
105	-	4.3	-	-	rabbit(Di)	70
75	73	5.1	5	-	dog	161
206	-	7.0	1	30	rat	99
240	60	8.5	10	V	human	139
213	-	10.0	1	30	rat	99
158	122	10.7	-	-	human	66
218	61	15.0	12	V	human	116
-	51	15.0	-	V	human	83
229	-	15.0	1	30	rat	99
305	57	15.0	5	V	rat	115 <sup>2</sup>
310	50	15.0	10	V	rat	43, 44, 45, 80
192	108	20.0	3	40	human	72
192	105	20.0	8	40	pig	72
240	-	20.0	1	30	rat	99
221	173	20.0	6	40	rat	72
-	105	22.5	32	-	human	67
133	-	22.5	36	-	human	67
148	-	24.3	4	23 <sup>4</sup>	human	52
191	-	24.3	2	23	human(B)	52
190	-	24.3	-	24	rat	87
144	-	30.0	8	-	human	92
320	-	30.0	1	30	rat	99
320	-	45.0	1	30	rat	99
-	165	60.0	2	22	hum(BLo, 61%)	145
-	52	60.0	2	22	hum(BSh, 38%)	145
200	-	60.0	-	24	human(B)	25
245	-	60.0	3	27	mouse	4
279	-	100.0	5	26	human	41, 42

Table 8. Breast

T1	T2	Freq	N	T	Species	Ref
126	-	1.8	22	-	human	138
337	-	13.6	4	-	rat(Lac)	17
447	46	22.5	12	-	human	67
554	46	22.5	11	-	human	67
510	-	24.0	6	-	human	109
191	-	24.3	2	23	human(Fat)	52
501	-	30.0	-	25	human	8
373	47	30.0	-	25	mouse(P)	6, 9
682	36	30.3	7	25	human	12, 113
380	39	30.3	5	25	mouse(P)	10, 12, 73
357	47	30.3	8	25	mouse(P)	12, 76
275	84	30.3	22	25	mouse(Vgn)	9, 11, 12
-	155	60.0	-	22	hum(17Lo, 62%)	145
-	52	60.0	-	22	hum(17Sh, 38%)	145
-	182	60.0	-	22	hum(65Lo, 59%)	145
-	57	60.0	-	22	hum(65Sh, 41%)	145
-	157	60.0	-	22	hum(75Lo, 60%)	145
-	50	60.0	-	22	hum(75Sh, 40%)	145
907	-	60.0	15	24	human	25
200	-	60.0	15	24	human(Fat)	25
-	105	60.0	26	22	human(Lo)	146
-	23	60.0	26	22	human(Sh)	146
367	-	100.0	5	26	human	41
978	-	100.0	1	26	human(Lac)	41
980	-	100.0	4	-	rat(Lac)	17

Table 9. Lung

T1	T2	Freq	N	T	Species	Ref
293	-	2.5	6	20	rabbit	105
268	-	4.3	-	V	rabbit	70
423	-	4.3	-	V	rabbit	70
-	33	4.3	-	V	rabbit	70
374	98	5.1	6	-	dog	161
576	-	10.7	2	RT	rat	33
-	47	15.0	1	25	mouse	59
-	50	15.0	1	25	mouse	59
756	139	20.0	3	40	human	72
844	87	20.0	8	40	pig	72
586	78	20.0	6	40	rat	72
534	92	22.5	22	-	human	101
535	87	22.5	17	-	human	69
544	91	22.5	11	-	rat	68
403	-	24.0	2	RT	human	84
491	-	24.0	3	RT	mouse	84
700	-	24.0	-	-	rabbit	109
800	-	24.0	-	-	rabbit	109
655	-	24.0	6	23	rabbit	105
587	-	25.3	3	RT	rat	37
-	71	25.6	5	33	hamster	103
690	-	25.6	10	25	rat, cow	102
657	-	30.0	1	25	mouse	59
641	-	30.0	6	25	mouse	59
670	-	32.0	6	25	chicken	136
788	-	100.0	5	26	human	41, 42

only a change of approximately 10% in long and short breast tissue  $T_2$  components over a 24 h period.

Authors reporting dual  $T_1$  components note contrary behavior of both components with time after excision. Chang *et al.*<sup>35</sup> measured an increase in the long rat muscle  $T_1$  component to a maximum of about 16% at 3 h after excision. This was followed by a reduction to a level 5% above the initial value at 4 h after excision, where it remained constant for 27 h. The short  $T_1$  component remained constant within 2% for the entire duration of the experiment. Sandhu and Friedmann<sup>141</sup> observed similar results, albeit on newt tails, except the long component increased 36% after 3 h and the short component declined 5% over 5 h postmortem. The opposite behavior in  $T_1$  components of mouse liver measured *in vivo*, at 2.5 and at 3.5 h postmortem is indicated by Barroilhet and Moran.<sup>5</sup> Their results showed that the long  $T_1$  component declined up to about 25%, whereas the short component first decreased about 10% then increased more than 10% after death. Their *in vivo* data for both components, however, show a 60% spread attributed to "intrinsic changes taking place in the tissue" which could easily explain their postmortem results. Moreover, while the behavior of multiple  $T_1$  components with time after excision may not be clear, both Chang *et al.* and Barroilhet and Moran data demonstrate that variations in the combined, average effective  $T_1$ 's are less than 10% during the periods studied.

A second class of experiments examined the effect of refrigeration of excised tissue samples prior to NMR measurements. Frey *et al.*,<sup>59</sup> Damadian *et al.*,<sup>42</sup> Parish *et al.*,<sup>126</sup> and Koenig *et al.*<sup>99</sup> all reported negligible or less than 10% variations in  $T_1$  relaxation times of animal and human tissues stored at 4–5 °C for periods of up to a week after excision. In addition, Parish *et al.*<sup>126</sup> and Goldsmith *et al.*<sup>68</sup> compared surgical and autopsy samples. In the former study, excised dog grey matter brain specimens placed on ice (surgical

Table 10. Fluids

T1	T2	Freq	N	T	Species	Fluid	Ref
3300	-	1.0	-	37	human	amniotic.fluid	15
3400	-	3.0	-	37	human	amniotic.fluid	15
3600	-	7.0	-	37	human	amniotic.fluid	15
-	2300	100.0	-	37	human	amniotic.fluid	15
275	-	1.7	-	V	human	bile	147
380	-	1.7	-	V	human	bile	148
888	-	2.5	3	20	rabbit	bile	105
383	339	5.1	3	-	dog	bile	161
890	80	8.5	6	V	human	bile	139
805	-	15.0	3	-	dog	bile	117
1078	-	24.0	3	23	rabbit	bile	105
303	-	1.0	1	35	rabbit	blood	99
385	-	1.6	1	35	rabbit	blood	99
355	-	1.7	20	V	human	blood	147,148,149,150
444	-	2.0	1	35	rabbit	blood	99
404	-	2.5	3	20	rabbit (Cl)	blood	105
372	-	2.5	3	20	rabbit (Hp)	blood	105
500	-	3.0	1	35	rabbit	blood	99
667	-	5.0	1	35	rabbit	blood	99
571	261	5.1	6	-	dog	blood	161
833	-	7.5	1	35	rabbit	blood	99
909	-	10.0	1	35	rabbit	blood	99
472	-	10.7	2	RT	rat	blood	33
1000	-	15.0	1	35	rabbit	blood	99
900	-	19.8	20	33	human	blood	100
893	362	20.0	3	40	human	blood	72
902	-	20.0	20	RT	mouse	blood	112
800	-	20.0	-	22	newt	blood	141
1111	-	20.0	1	35	rabbit	blood	99
901	251	20.0	6	40	rat	blood	72
800	-	24.0	-	-	rabbit	blood	109
867	-	24.0	3	23	rabbit (Cl)	blood	105
872	-	24.0	3	23	rabbit (Hp)	blood	105
920	-	32.0	6	25	chicken	blood	136
900	-	1.7	-	V	human	cerebrospinal.fl	148
675	-	1.7	-	V	human	cerebrospinal.fl	147
-	915	6.5	6	V	human	cerebrospinal.fl	3
1450	-	6.5	10	V	human	cerebrospinal.fl	32
1155	145	12.8	1	V	human	cerebrospinal.fl	157
175	-	2.5	3	20	rabbit	marrow	105
306	-	4.3	1	V	rabbit	marrow	70,71
-	59	4.3	-	V	rabbit	marrow	70
-	17	4.3	-	V	rabbit	marrow	70
359	-	4.3	1	V	rabbit	marrow	70
271	-	4.3	1	V	rabbit	marrow	70
280	80	8.5	10	V	human	marrow	139
380	70	8.5	10	V	human (Verte)	marrow	139
320	80	12.8	4	V	human	marrow	157
420	50	15.0	16	V	human (Verte)	marrow	116
130	-	24.0	-	-	human	marrow	109
200	-	24.0	-	-	rabbit	marrow	109
202	-	24.0	3	23	rabbit	marrow	105
803	-	25.0	5	-	human	marrow	132
408	-	32.0	6	25	chicken	marrow	136
1000	-	1.7	-	V	human	urine	148
800	-	1.7	-	V	human	urine	147
2650	2600	5.1	3	-	dog	urine	161
2200	570	8.5	6	V	human	urine	139
3740	159	15.0	5	V	rat	urine	115



Table 11. Miscellaneous

T1	T2	Freq	N	T	Species	Tissue	Ref	T1	T2	Freq	N	T	Species	Tissue	T1	
277	-	2.5	3	20	rabbit	adrenal	105	1291	-	100.0	1	26	human	pineal-gland	41.42	
253	79	5.1	5	-	dog	adrenal	161	1000	-	24.3	1	26	human	placenta	39	
448	-	24.0	3	23	rabbit	adrenal	105,109	200	-	1.7	-	-	V	human	prostate	147
585	-	24.3	1	26	human	adrenal	39	288	-	1.7	-	-	V	human	prostate	72
608	-	100.0	5	26	human	adrenal	41.42	808	98	20.0	3	40	human	prostate	41.42	
860	90	8.5	10	V	human	aorta	139	767	-	24.3	1	26	human	prostate	39	
211	-	2.5	3	20	rabbit	aortic-arch	105	803	-	100.0	2	26	human	prostate	41.42	
451	-	24.0	3	23	rabbit	aortic-arch	105,109	600	-	24.0	-	-	rabbit	rectum	109	
212	47	5.1	4	-	dog	artery	161	245	-	2.5	3	20	rabbit	rectum-wall	105	
600	-	24.0	3	26	human	bladder	109	492	-	24.3	3	23	rabbit	rectum-wall	105	
891	-	100.0	3	-	human	bladder	41.42	400	-	24.0	-	-	rabbit	salivary-gland	109	
200	-	1.7	-	V	human	bone	90	384	-	60.0	8	27	mouse	scalp	157	
125	-	24.0	1	-	human	bone	109	198	-	12.8	4	V	human	scalp	105	
200	-	24.0	1	-	rabbit	bone	109	235	-	2.5	3	20	rabbit	skin	59	
554	-	100.0	10	26	human	bone	41.42	450	-	35	15.0	2	25	mouse	skin	109
167	-	2.5	3	20	rabbit	carotid-artery	105	450	-	24.0	6	-	human	skin	109	
364	-	24.0	3	23	rabbit	carotid-artery	105	193	-	24.0	3	23	mouse	skin	84	
500	-	24.0	3	23	rabbit	carotid-wall	109	328	-	24.0	3	23	rabbit	skin	105	
87	-	100.0	4	26	human	cervix	41.42	423	-	24.3	2	23	human	skin	52	
227	-	2.5	3	20	rabbit	colon	105	225	-	24.3	5	23	mouse	skin	142	
366	64	22.5	16	-	human	colon	101	272	-	25.3	3	33	rat	skin	37	
388	56	22.5	12	-	rat	colon	68	-	-	65	25.6	5	33	hamster	skin	103
475	-	24.0	1	-	human	colon	84	390	-	30.0	5	25	mouse	skin	59	
300	-	24.0	1	-	rabbit	colon	109	722	-	30.0	1	25	mouse	skin	59	
466	-	24.0	3	23	rabbit	colon	105	616	-	100.0	8	26	human	skin	41	
552	-	24.3	2	23	human	colon	52	224	-	2.5	3	20	rabbit	small-intestine	84	
398	-	25.3	3	23	human	colon	37	306	-	24.0	2	23	mouse	small-intestine	109	
641	-	100.0	12	26	human	colon	41.42	400	-	24.0	-	-	rabbit	small-intestine	105	
202	-	2.5	3	20	rabbit	diaphragm	105	481	-	24.0	3	23	rat	small-intestine	40	
458	-	24.0	3	23	rabbit	diaphragm	105	584	-	24.3	2	23	human	small-intestine	52	
700	-	24.0	1	-	rabbit	diaphragm	109	325	-	2.5	3	20	human	small-intestine	41.42	
936	-	100.0	1	26	human	diaphragm	41.42	464	-	24.0	3	23	rabbit	spinal-cord	105	
309	-	2.5	2	20	rabbit	epididymus	105	464	-	24.0	3	23	rabbit	spinal-cord	105	
625	-	24.0	2	23	rabbit	epididymus	105,109	227	-	2.5	3	20	rabbit	stomach	59	
530	-	2.5	3	20	rabbit	esophagus	105	464	-	2.5	3	20	mouse	stomach	109	
534	-	24.0	3	23	rabbit	esophagus	105	468	-	35	15.0	2	25	mouse	stomach	109
804	-	100.0	5	26	human	esophagus	41.42	400	-	24.0	-	-	rabbit	stomach	105	
329	-	60.0	8	27	mouse	eyelids	4	468	-	24.0	3	23	rat	stomach	105	
1247	-	100.0	1	26	human	fallopiian-tube	41.42	270	-	24.0	5	-	human	stomach	39	
269	55	15.0	-	-	human	femoral-heads	79	541	-	24.3	1	26	human	stomach	37	
416	58	22.5	28	-	human	gastrointestinal	68	372	-	25.3	3	23	rat	stomach	59	
201	-	2.5	3	20	rabbit	infer-venacava	105	294	-	30.0	6	25	mouse	stomach	59	
316	-	24.0	3	23	rabbit	infer-venacava	105	318	-	30.0	1	25	mouse	stomach	41.42	
2623	48	15.0	4	V	human	intervertebr-disc	116	765	-	100.0	8	26	human	stomach	59	
-	36	15.0	2	25	mouse	intestine	59	463	-	2.5	2	20	rabbit	testis	105	
-	-	-	-	-	-	intestine	59	410	111	5.1	2	-	dog	testis	161	
366	-	30.0	7	25	mouse	intestine	59	410	-	10.7	2	23	rat	testis	33	
361	-	30.0	1	25	mouse	intestine	59	674	-	10.7	2	23	rat	testis	72	
864	107	15.0	3	V	human	ligament/tendon	116	974	153	20.0	3	40	human	testis	84	
725	91	20.0	3	40	human	lymph-node	72	205	-	24.0	1	23	mouse	testis	105	
720	-	100.0	6	26	human	lymph-node	41.42	855	-	24.0	2	23	rabbit	testis	109	
1050	75	100.0	5	-	mouse	lymph-node	91	800	-	24.0	-	-	human	testis	52	
200	-	24.0	-	-	rabbit	mesentery	109	705	-	24.3	4	23	human	testis	39	
111	58	5.1	3	-	dog	nerve	161	1010	-	24.3	1	26	human	testis	41.42	
300	-	24.0	-	-	rabbit	nerve	109	1200	-	100.0	4	26	human	testis	39	
557	-	100.0	2	26	human	nerve	41.42	809	-	24.3	1	26	human	thymus	72	
310	-	2.5	1	20	rabbit	ovary	105	605	102	20.0	3	40	human	thyroid	109	
380	126	5.1	2	-	dog	ovary	161	500	-	24.0	-	-	rabbit	thyroid	39	
600	-	24.0	3	-	human	ovary	109	586	-	24.3	1	26	human	thyroid	52	
573	-	24.0	1	23	rabbit	ovary	105	409	-	24.3	2	23	human	thyroid	41.42	
989	-	100.0	5	26	human	ovary	161	882	-	100.0	7	26	human	thyroid	41.42	
190	-	1.7	40	V	human	pancreas	147,148,150	584	61	20.0	3	40	human	tongue	72	
231	43	5.1	3	-	dog	pancreas	161	560	58	20.0	8	40	pig	tongue	72	
290	60	8.5	-	V	human	pancreas	139	199	-	2.5	3	20	rabbit	trachea	105	
218	-	10.7	2	23	rat	pancreas	72	276	-	24.0	3	23	rabbit	trachea	105,109	
572	189	20.0	3	40	human	pancreas	93	693	-	100.0	1	26	human	trachea	41.42	
300	-	24.0	3	-	rabbit	pancreas	109	172	-	2.5	3	20	rabbit	ureter	105	
320	-	24.3	3	26	human	pancreas	39	252	-	24.0	3	23	rabbit	uterus	105,109	
605	-	100.0	10	26	human	pancreas	41.42	924	-	100.0	4	26	human	uterus-wall	105	
234	-	2.5	3	20	rabbit	parotid-gland	105	296	-	2.5	1	23	rabbit	uterus-wall	105	
350	30	8.5	-	V	human	parotid-gland	139	653	-	24.0	1	23	rabbit	uterus-wall	105	
340	-	24.0	3	23	rabbit	parotid-gland	105	1019	-	100.0	2	26	human	vagina	41.42	
476	-	100.0	1	26	human	peritoneum	41.42	550	-	24.0	2	-	human	vein	109	

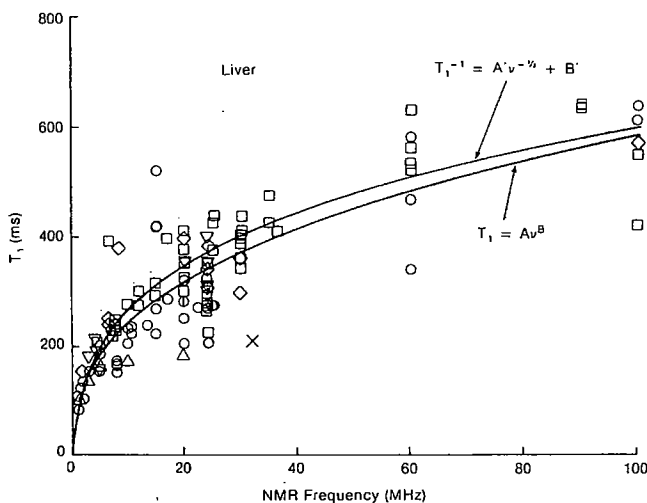


FIG. 1.  $T_1$  dispersion data for liver fitted to  $T_1 = Av^B$  with  $A = 0.000534$ ,  $B = 0.3799$  and standard deviation from the curve of 22% using a method of least squares. A least-squares fit to the Escanye *et al.* expression

$$T_1^{-1} = A'v^{-1/2} + B'$$

gave the same standard deviation and a best fit with  $A' = 9807$ ,  $B' = 0.689$ . These parameters are the same as determined previously with less data (Ref. 54). The mean cited standard deviation for each point expressed as a percentage of the  $T_1$  value is about  $(9 \pm 5)\%$ .

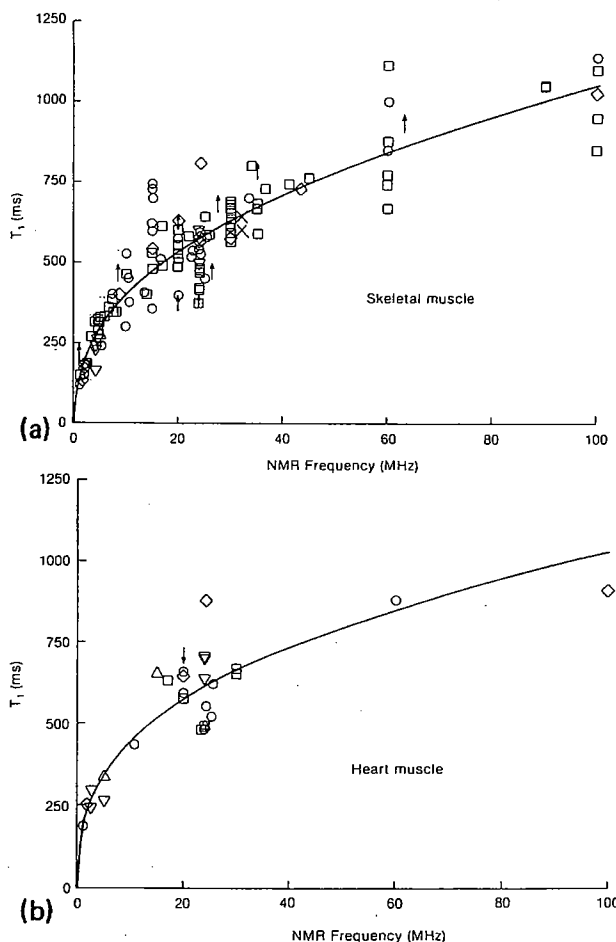


FIG. 2. (a)  $T_1$  dispersion data for skeletal muscle and (b) heart muscle fitted to  $T_1 = Av^B$ . Fitting parameters are listed in Table 12. The mean cited standard deviation for each point expressed as a percentage of the  $T_1$  value is about  $(5 \pm 3)\%$ .

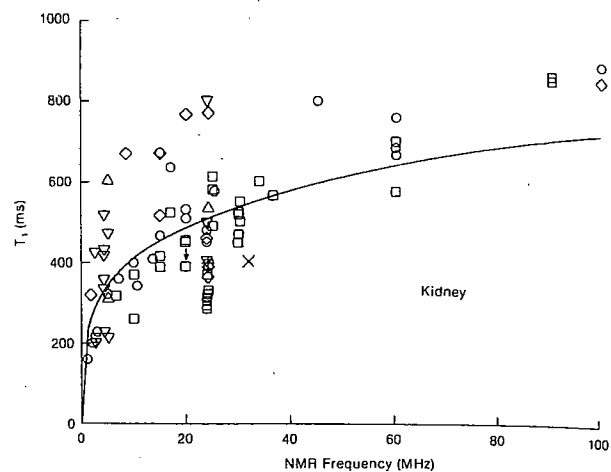


FIG. 3.  $T_1$  dispersion data for kidney fitted to  $T_1 = Av^B$  with parameters listed in Table 12. Cortex and medulla are undifferentiated. The mean cited standard deviation for each point expressed as a percentage of the  $T_1$  value is about  $(6 \pm 5)\%$ .

group) were compared with tissues taken from an intact carcass (autopsy group), and excised tissue refrigerated overnight. No changes in  $T_1$  greater than the experimental error (8%) were observable in any of these tissues, even after two days. The Goldsmith group observed no difference between autopsy and surgical rat muscle, liver, and lung  $T_1$ 's and  $T_2$ 's within experimental error (6%–16%). However, a 20% difference in colon  $T_1$ 's was noted and attributed to intraperitoneal injection of anesthetic. In contrast, Beale implored researchers to "resist the temptation to place tissues on ice or in the refrigerator,"<sup>8</sup> but cited decreases in  $T_1$  of only 8%, 8%, 18%, and 14% in muscle, breast, nipple, and lymph node, respectively, following 48 h refrigeration. Also Small *et al.*<sup>145</sup> measured up to a 30% decline in both long and short  $T_2$  components of breast tissue following 24 h refrigeration, compared with the decrease of only 10% noted above with the samples kept at room temperature for the same period.

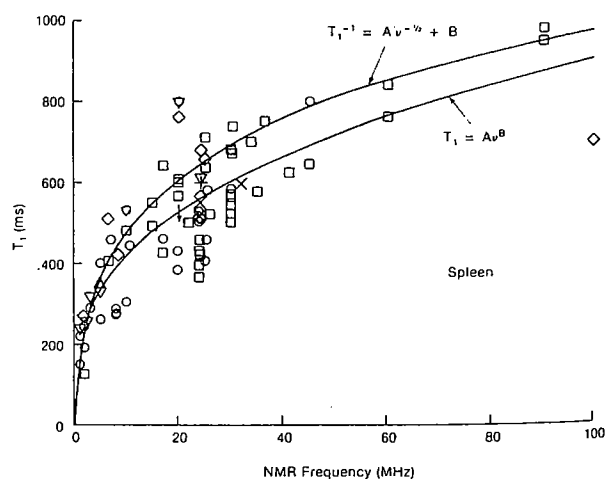
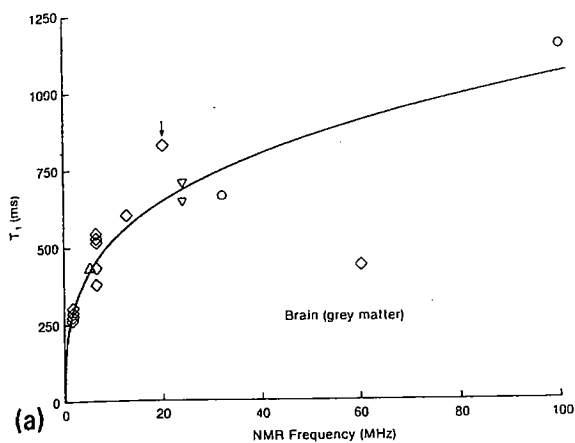


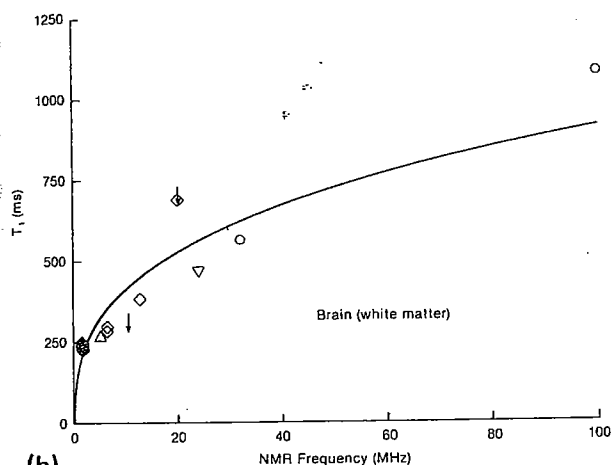
FIG. 4.  $T_1$  dispersion data for spleen fitted to  $T_1 = Av^B$  with Table 12 fitting parameters (standard deviation = 19%). A best fit to Escanye *et al.*'s equation,

$$T_1^{-1} = A'v^{-1/2} + B'$$

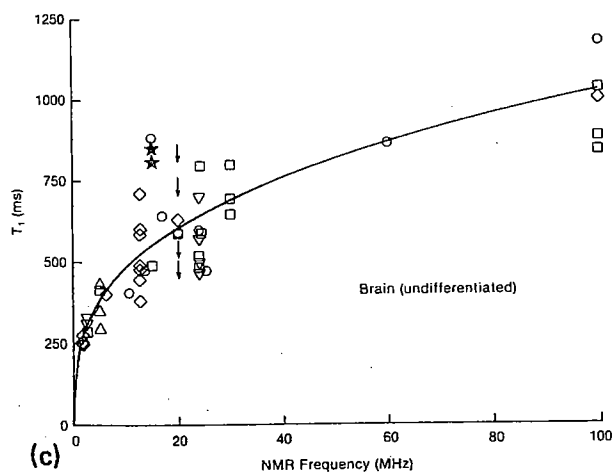
with  $A' = 5036$ , and  $B' = 0.520$ , gave a 21% standard deviation (Ref. 54). The mean cited standard deviation for each point expressed as a percentage of the  $T_1$  value is about  $(8 \pm 5)\%$ .



(a)



(b)



(c)

FIG. 5. (a)  $T_1$  dispersion data for grey brain matter, (b) white brain matter, and (c) other undifferentiated brain tissue, fitted to  $T_1 = Av^B$  with Table 12 fitting parameters. The mean cited standard deviation for each point expressed as a percentage of the  $T_1$  value is about  $(7 \pm 4)\%$ .

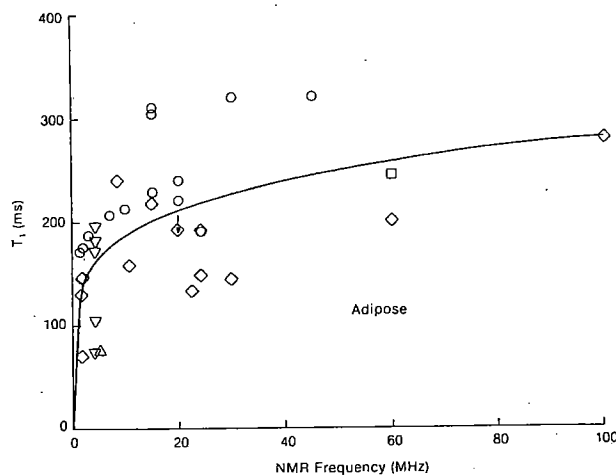


FIG. 6.  $T_1$  dispersion data for adipose fitted to  $T_1 = Av^B$  with Table 12 fitting parameters. The mean cited standard deviation for each point expressed as a percentage of the  $T_1$  value is about  $(12 \pm 6)\%$ .

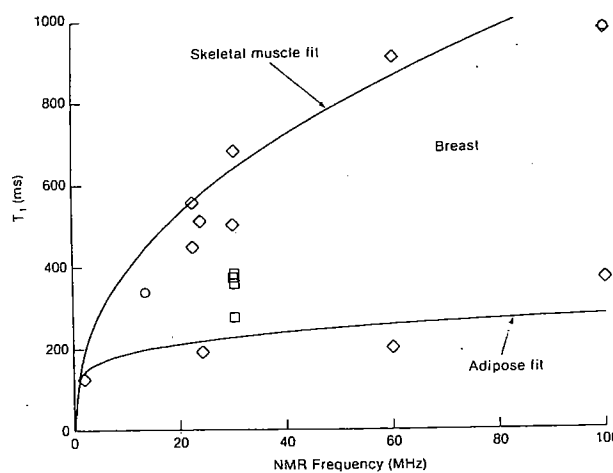


FIG. 7.  $T_1$  dispersion data for breast tissue. The best-fit curves from skeletal muscle and adipose are superimposed for comparison. The mean cited standard deviation for each point expressed as a percentage of the  $T_1$  value is about  $(12 \pm 13)\%$ .

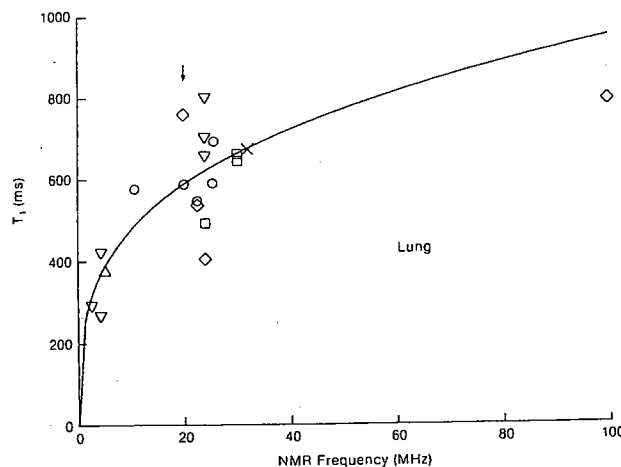


FIG. 8.  $T_1$  dispersion data for lung tissue fitted to  $T_1 = Av^B$  with Table 12 fitting parameters. The mean cited standard deviation for each point expressed as a percentage of the  $T_1$  value is about  $(10 \pm 10)\%$ .

Table 12  
MEAN  $^1\text{H}$  TISSUE  $T_1$  and  $T_2$  RELAXATION TIMES

Tissue	$T_1$			$T_2$	
	A	B	SD (%)	$T_2$ (ms)	SD (ms)
Muscle					
skeletal	.000455	.4203	18	47	13
heart	.00130	.3618	16	57	16
Liver	.000534	.3799	22	43	14
Kidney <sup>3</sup>	.00745	.2488	27	58	24
Spleen	.00200	.3321	19	62	27
Adipose	.0113	.1743	28	84	36
Brain					
grey matter	.00362	.3082	17	101	13
white matter	.00152	.3477	17	92	22
unspecified	.00232	.3307	19	76	21
Lung	.00407	.2958	19	79	29
Marrow <sup>4</sup>				59	24
Breast <sup>5</sup>				49	16

1.  $T_1 = A \nu^B \pm \text{SD } \%$ , where  $\nu = ^1\text{H}$  NMR frequency in Hz, SD = standard deviation expressed as a percentage of  $T_1$ ,  $T_1$  in sec.
2. Assumes  $T_2$  is independent of frequency. Multicomponent data is omitted from the computations.  $T_2$  is in ms. SD = standard deviation in ms.
3. Averages medulla and cortex.
4. Insufficient data for a  $T_1$  fit.
5. Use skeletal muscle and/or adipose  $T_1$  fits.

#### D. *In vitro* versus *in vivo* human measurements

*In vivo* relaxation time measurements from macroscopically homogeneous tissue types have arguably only become possible with the recent innovation of NMR imaging techniques. Tabulated  $^1\text{H}$  human *in vivo* relaxation data are available only up to 15 MHz with grey and white brain matter having the most points. Figure 12 compares the human *in vivo* brain  $T_1$  dispersions with the computed best-fit grey and white matter curves from Fig. 5. Note that data conform to the curves within the specified standard deviation (Table 12), and significant point scatter exists despite the constancy of species, temperature, tissue status, and averaged sample heterogeneity represented by the points. There may be a tendency for slightly elevated  $T_1$  values measured *in vivo* compared to *in vitro* (see Sec. IV C), but such trends are concealed from the curve by the noise. For example, Gore *et al.*<sup>70</sup> and Ling and Foster<sup>104</sup> observe an approximately 13% decrease in the  $T_1$ 's of muscle of dead intact rabbits compared to the living animals.

#### E. Dependence on age

Drastically elevated relaxation times are reported for neonatal tissue<sup>30,77,94,96,97,103,114,148</sup> persisting a few weeks in animals to at least several months after birth in humans. Hazlewood *et al.*<sup>77</sup> noted that immature muscle  $T_1$  and  $T_2$  (< 10 days old) were, respectively, 1.7 and 2.7-fold the mature values (> 40 days). They proposed that the fraction of

"ordered water" increases during postnatal development. Similarly, Kiricuta *et al.*<sup>96,97</sup> reported immature rat brain, heart, and liver  $T_1$  elevations of 110%, 50%, and 40%, respectively, attributable to an approximately 14% increase in water content in neonates compared to adults. Lewa and Zbytniewski<sup>103</sup> measured 8%–40% increases in the  $T_2$ 's of liver, spleen, and skin in 3-month-old hamsters compared to 6-month-old animals. Buonnano *et al.*<sup>30</sup> observed that neonatal gerbil brain  $T_1$ 's changed from 1.83 to 1.26 s in three weeks time after birth at which point "adult levels" are reached (Fig. 13). Misra *et al.*<sup>114</sup> recorded muscle  $T_1$ 's of 1.24 s in 18-day embryo and 1-day postnatal chickens which declined to 0.746 and 0.647 s at 8 and 16 days postnatal, respectively (Fig. 13).

Some human fetal  $T_1$ 's were tabulated by Kasturi *et al.*<sup>94</sup>: 0.721, 1.05, and 0.993 at 25 MHz for liver, lung, and kidney, respectively. These are about double the mean (adult) values plotted in Figs. 1, 8, and 3. Also Smith<sup>148</sup> noted " $T_1$  images of the neonatal brain (of a 9-week-old child) show a uniformly long  $T_1$ , due to the absence of myelin, and cannot differentiate between grey and white matter, the  $T_1$  of both being markedly elongated at 390–400 ms" (at 1.7 MHz).

Evidence for relatively minor fluctuations in  $T_1$  with circadian rhythm also exists. De Certaines *et al.*<sup>46</sup> observed a statistically significant 12% variation in rat liver  $T_1$ 's excised as a function of time, with a peak at midday and minimum at dawn. No substantial corresponding fluctuations in either  $T_2$  or water content were measured.

## IV. COMPARISON WITH THEORY

### A. Spin-lattice relaxation

The liquidlike  $^1\text{H}$   $T_1$  frequency dispersions observed in biological tissue can involve both intramolecular and intermolecular dipolar interactions of macromolecules and water molecules of the general form

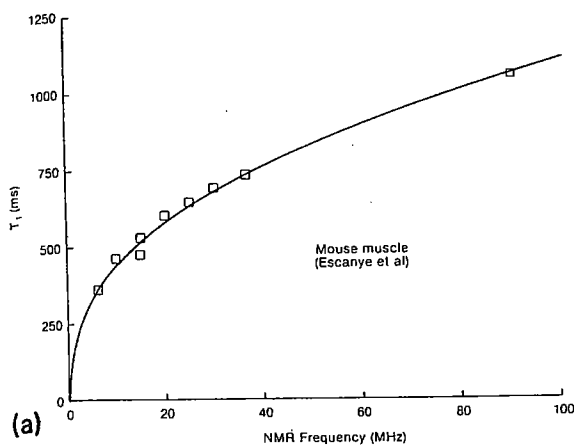
$$\frac{1}{T_1} = \frac{9}{8} \gamma^4 \bar{h}^2 [J^1(\nu) + J^2(2\nu)], \quad (3)$$

with  $\gamma = 2.675 \times 10^8 \text{ s}^{-1} \text{ T}^{-1}$ ,  $\bar{h} = 1.055 \times 10^{-34} \text{ Js}$ , and where  $J^1(\nu)$ ,  $J^2(2\nu)$  are spectral density functions for the various motions evaluated at the resonance frequency and at twice that frequency.<sup>1</sup> Intramolecular processes involve mainly rotational motion with spectral density functions

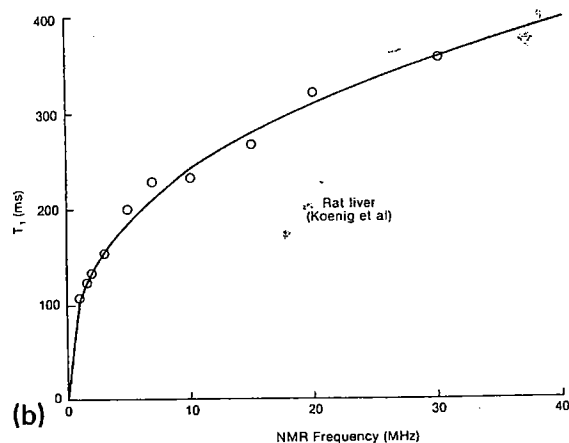
$$J^1(\nu) = \frac{J^2(\nu)}{4} = \sum_{i,j} \frac{4C_{ij}}{15r_j^6} \left[ \frac{\tau_{ij}}{1 + 4\pi^2 \nu^2 \tau_{ij}^2} \right], \quad (4)$$

where  $r_j$  is an intramolecular (H–H) distance between nuclear dipoles,  $C_{ij}$  are weighting coefficients independent of frequency, and the  $\tau_{ij}$  are correlation times for the  $i$ th characteristic mode of motion of the  $j$ th intramolecular dipole pair.<sup>1,57,64,98,159</sup> Ignoring macromolecular hydrogen enables omission of the  $j$  summation so the  $r_j$  becomes the (fixed) separation between hydrogens in water molecules.

Many established models invoke two components of water in tissue undergoing rapid exchange relative to the NMR observation time: a large free water compartment and a bound water compartment hydrogen bonded to macromolecules or hydration layers.<sup>38,47,54,55,57,60,61,75,92,96,98,140</sup> The observation of a nonfreezing water component in many tissues,



(a)



(b)

FIG. 9. (a)  $T_1$  dispersion data for mouse muscle from Escanye *et al.* (Ref. 54), fitted to  $T_1 = Av^B$  with  $A = 0.000\ 645$ ,  $B = 0.4044$ , and standard deviation 3.7%. The Escanye *et al.* fit,

$$T_1^{-1} = A'v^{-1/2} + B'$$

with  $A = 6225$ ,  $B = 0.300$  yielded the same standard deviation. (b)  $T_1$  dispersion data for rat liver from Koenig *et al.* (Ref. 99) fitted to  $T_1 = Av^B$  with  $A = 0.000\ 741$ ,  $B = 0.3592$ , and standard deviation 3.9%. The latter data were derived from relaxation rate curves and probably contains reading errors.

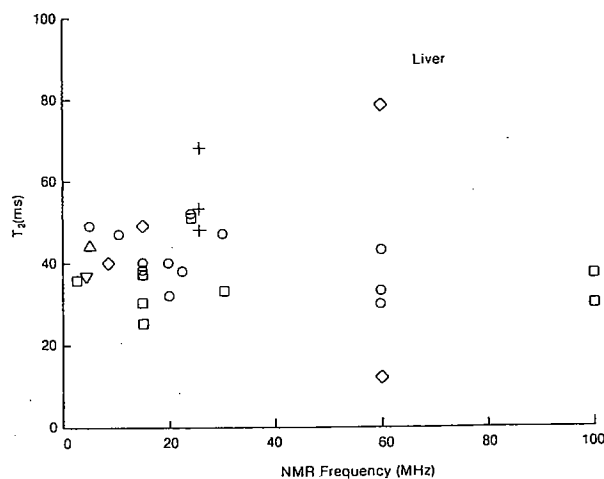


FIG. 10.  $T_2$  dispersion data for liver omitting multicomponent measurements. The mean cited standard deviation for each point expressed as a percentage of the  $T_2$  value is about  $(10 \pm 10)\%$ .

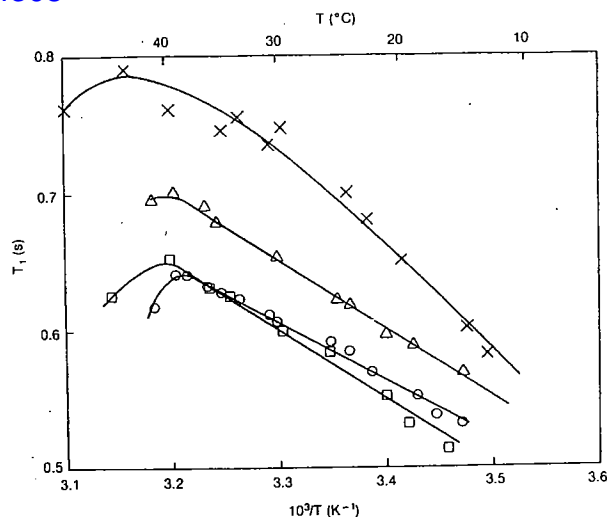


FIG. 11. The temperature ( $T$ ) dependence of rat and cow  $T_1$  values at 25.6 MHz from Lewa and Majewska (Ref. 102).  $\circ$  spleen;  $\triangle$  heart;  $\times$  lung;  $\square$  muscle.

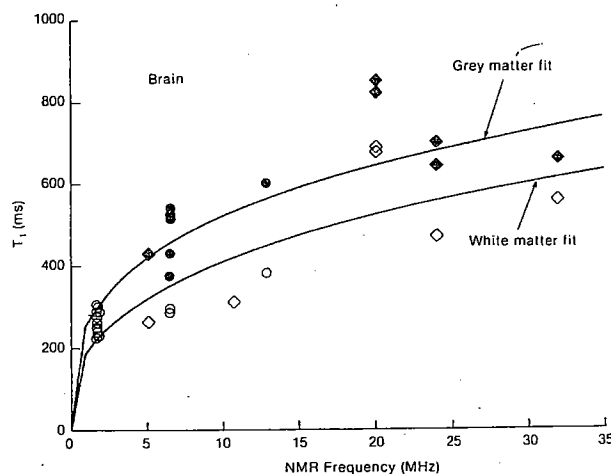


FIG. 12.  $T_1$  dispersion data for grey and white brain matter comparing human *in vivo*, with all of the *in vitro* measurements. Circles and diamonds denote *in vivo* and *in vitro* data, respectively; shaded symbols correspond to grey matter. Curves of best fit from Figs. 5(a) and 5(b) are shown for comparison. The mean cited standard deviation for each point expressed as a percentage of the  $T_1$  values are about  $(7 \pm 4)\%$ .  $\circ$  white matter *in vivo*;  $\bullet$  grey matter *in vivo*;  $\diamond$  white matter *in vitro*;  $\blacklozenge$  grey matter *in vitro*.

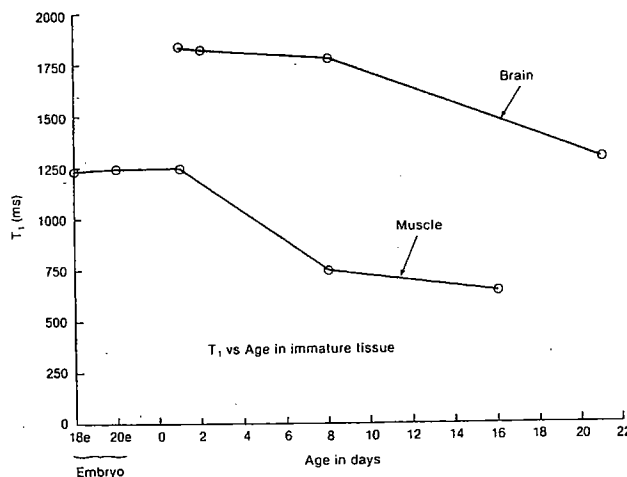


FIG. 13.  $T_1$ 's of neonatal gerbil brain at 150 MHz from Buonanno *et al.* (Ref. 30), and chicken muscle at 20 MHz from Misra *et al.* (Ref. 114), as a function of age. The cited standard deviations for both data sets expressed as a percentage of the  $T_1$  values is about 1%.



often directly identified with the bound phase, is key evidence for this FETS model.<sup>111</sup> A hypothesis, due to Ling, in which all intracellular water exists in an ordered, polarized state has also been invoked.<sup>40,63,75</sup>

The relaxation rate in the FETS model is a weighted average of the two states:

$$\frac{1}{T_1} \sim \frac{b}{T_{1b}} + \frac{1-b}{T_{1f} + \tau_e}, \quad (5)$$

where  $T_{1b}$  is the  $T_1$  of the bound fraction ( $b \ll 1$ ) of water,  $T_{1f}$  the  $T_1$  of the free water fraction, and  $\tau_e$  is the (short) residence time of water in the restricted compartment.<sup>75,57</sup>  $T_{1f}$  is approximately equal to the  $T_1$  of tap water ( $\sim 2-3$  s) and constitutes  $\sim 75\%-99\%$  of the total observed water ( $b \sim 0.01-0.25$ ). Free water undergoes rapid translational and rotational diffusion, that is,  $4\pi^2 \nu^2 \tau_f^2 \ll 1$  for  $\nu \leq 100$  MHz with a single free water correlation time  $\tau_f \sim 1$  ps. Thus  $T_{1f}$  is essentially independent of frequency. The frequency dependence of the measured  $T_1$  is therefore determined by  $T_{1b}$ . That this is so for biological tissues is shown by  $T_1$  experiments performed by Fung at 5, 30, and 100 MHz in which  $b$  is varied by soaking tissue samples in solutions of different osmolarity.<sup>61,142</sup> The extrapolated intercept from Eq. (5) is identified as  $\sim 1/T_{1f}$  provided that  $\tau_e \ll T_{1f}$ , and corresponds to  $T_{1f} \sim 1.7$  s independent of frequency.<sup>61</sup> Also Escanye *et al.*<sup>54</sup> determined

$$T_{1f} \sim 1.8 \left[ \begin{array}{c} + 1.3 \\ - 0.5 \end{array} \right] \text{ s}$$

independent of frequency from 6.7 to 90 MHz as a tissue average over normal and cancerous muscle, spleen, liver, and kidney. This results from equating Eq. (5) with their dispersion Eq. (2) wherein  $B' \sim (1-b)/T_{1f}$ .

The simplest model characterizes the rate  $1/T_{1b}$  by isotropic rotational motion and a single correlation time, implying, from Eqs. (3)–(5),  $T_1 \propto \nu^2$ . Such behavior was fitted by Knispel *et al.*<sup>98</sup> to  $T_1$  data measured over 17–45 MHz, but this model does not satisfactorily cope with the extended 1–100 MHz range investigated here.<sup>54</sup> Thus, multiple or continuously distributed correlation times are required. A dual

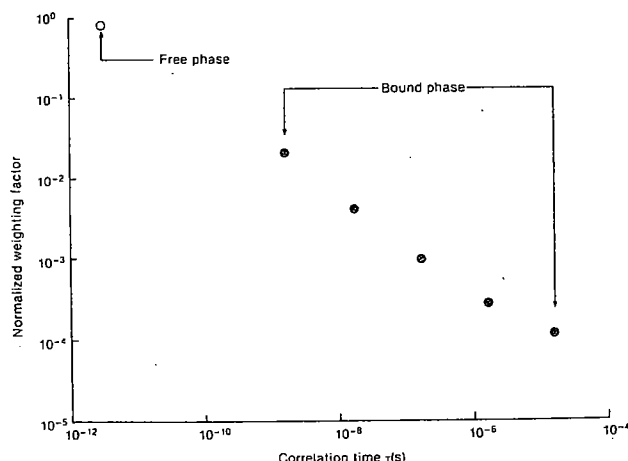


FIG. 14. Discrete distribution of six correlation times and their weighting factors fitted by Finch and Homer (Ref. 57) to frog muscle  $T_1$  and  $T_{1\rho}$  dispersions using Eqs. (3) and (4), and omitting the  $j$ -summation.

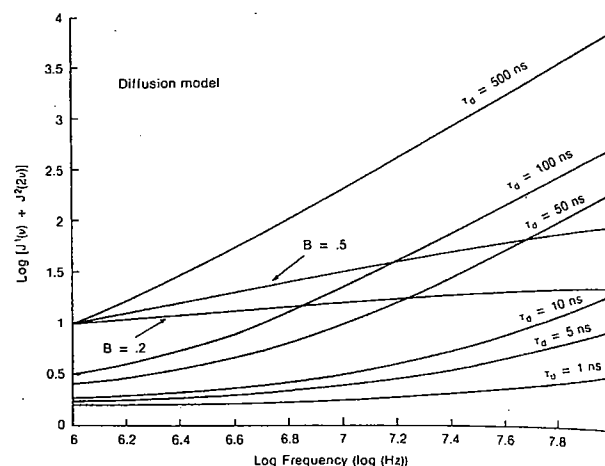


FIG. 15. Investigation of the isotropic diffusion model of  $T_1$  relaxation in the bound phase (Ref. 54). The curves were obtained by numerical integration of Eq. (7) as a function of frequency from 1–100 MHz with different diffusion correlation times  $\tau_d$ . Since

$$1/T_1 \propto J^1(\nu) + J^2(2\nu),$$

the model satisfies the empirical Eqs. (1) and (2) when a  $\tau_d$  is found for which the curves are linear. Straight lines with gradients of 0.2 and 0.5 depict the actual range of  $B$  values observed (Table 12).

correlation time model involving intramolecular interactions with anisotropic reorientation of bound water fitted Escanye *et al.*'s data,<sup>54</sup> but required excessive free water fractions in the range  $0.98 \leq 1-b < 1$ . Here, one correlation time would correspond to rapid motion about an axis perpendicular to the H–H direction, and the other to slow reorientation of this axis under the influence of macromolecular motion.<sup>159</sup>

Whilst correlation times associated with intramolecular interactions are dominated by rotation, intermolecular interactions involve mainly translational motion. However, rotation and translation of water molecules in water are arguably coupled, suggesting that the same correlation times could be used to characterize both motions. This offers some justification for floating  $C_{ij}$  and  $r_j$  to intermolecular/intramolecular averages, and computing  $T_{1b}$  from Eqs. (3)–(5) with a single summation over the  $i$  correlation times.<sup>57</sup> Finch and Homer fitted such a model to frog muscle dispersion data to within experimental accuracy (5%), albeit using nine fitting parameters, including five discrete correlation times for the bound compartment and a single correlation time for the free compartment, and only 19 data points.<sup>57</sup> The resultant weighting coefficients ( $C_i$ ) are plotted against correlation time in Fig. 14. The results appear consistent with the existence of several hydration layers bonded to macromolecules with increasing mobility in outer layers, and suggest a distribution of residence times ( $\tau_e$ ) rather than the single value assumed. However, the estimates of  $(1-b)$  and  $\tau_e$  seem somewhat excessive at 0.97 and 0.8 ms, respectively.

Models incorporating distributed correlation times for the molecular motion of the bound water fraction were proffered by Held *et al.*,<sup>78</sup> Fung and McGaughy,<sup>64</sup> and Escanye *et al.*<sup>54</sup> All attempted a log-Gaussian distribution function of intramolecular correlation times for rotation

$$g(\tau) = \frac{\alpha}{\tau\sqrt{\pi}} \exp \left\{ - \left[ \alpha \ln \left| \frac{\tau}{\tau_0} \right| \right]^2 \right\}, \quad (6)$$

( $\alpha$ ,  $\tau_0$  empirically determined constants), not dissimilar from the discrete distribution of Fig. 14, to provide a good fit to frog muscle frequency dispersion data recorded between 3 kHz and 75 MHz. This requires replacement of the Eq. (4) summation by the integral  $\int g(\tau)d\tau$  which is then evaluated numerically,<sup>64</sup> again implicitly incorporating both intramolecular and intermolecular contributions by empirically fitting the parameters.

Escanye *et al.*<sup>54</sup> also proposed a model involving distributed correlation times to explain their fit to Eq. (2). In this model,  $T_1$  relaxation is dominated by intermolecular interactions that consist entirely of translational diffusion of bound tissue water treated as spheres. The spectral density functions for isotropic, uniform translational diffusion are

$$J^1(\nu) = \frac{J^2(\nu)}{4} = \frac{M}{dD} \int_0^\infty [J_{3/2}(u)]^2 \frac{u du}{u^4 + 4\pi^2 \nu^2 \tau_d^2}, \quad (7)$$

where  $M$  is the  $^1\text{H}$  spin density,  $J_{3/2}(u)$  is a Bessel function of order  $3/2$ ,  $u = rd$ ,  $r$  is the distance variable between diffusing molecules,  $d$  is the distance of closest approach,  $D$  is the diffusion coefficient and  $\tau_d = d^2/2D$  is the diffusion jump time.<sup>1,54</sup> Assuming  $d = 5 \text{ \AA}$  and a 50-ns jump time, the model<sup>54</sup> yields a bound water diffusion coefficient of  $2.5 \times 10^{-8} \text{ cm}^2 \text{ s}^{-1}$  that is about 400 times less than Hazelwood *et al.*'s bulk muscle tissue measurements.<sup>75,74</sup> However, the latter must be considered as free/bound fraction averages. Alternatively, Koenig *et al.*<sup>99</sup> used the heuristic Cole-Cole expression

$$\frac{1}{T_1} = \frac{1}{T_{1f}} + G + \frac{H [1 + (\nu/\nu_c)^{\beta/2} \cos(\pi\beta/4)]}{1 + 2(\nu/\nu_c)^{\beta/2} \cos(\pi\beta/4) + (\nu/\nu_c)^\beta}, \quad (8)$$

where  $G$ ,  $H$ ,  $\nu_c$ , and  $\beta$  are four fitting parameters to be determined.

Semiempirical multiparameter models such as these are susceptible to the criticism that given enough variables, success is virtually guaranteed, particularly since the experimental dispersions are apparently continuous, slow varying, and monotonic. Close scrutiny of predicted parameters is necessary to determine their physical relevance. Thus the relation,  $T_1 = A \nu^\beta$ , allowing the exponent to vary empirically, provides as good or better average fit to the tabulated data as the Escanye group's equation (Figs. 1 and 4), and an excellent, if not superior fit to the individual tissue dispersions of Escanye *et al.* and Koenig *et al.* (Fig. 9) with minimal fitting coefficients compared to Eq. (3)–(8). Although its physical significance is yet to be determined, the resemblance of Eq. (1) to the Escanye *et al.* isotropic diffusion model and Eq. (2) is undeniable. However, numerical evaluation of Eqs. (3) and (7) using similar values of  $\tau_d$ ,  $d$ , and  $D$  yields curves nonlinear in  $\log(T_1)$  versus  $\log(\nu)$  over 1–100 MHz, contrary to the requirements of both Eqs. (1) and (2) (Fig. 15). Therefore, either a distribution of diffusional correlation times are necessary, or intramolecular rotational contributions cannot be totally neglected.

Estimates of the relative importance of the intermolecular and intramolecular mechanisms to bound water relaxation are open to ambiguous interpretation. *A priori*, the  $r_j^{-6}$  dependence of the dipole-dipole interaction [Eq. (4)] strongly

favors dominance by intramolecular processes. However, both intermolecular and intramolecular models can be fitted to the  $T_1$  dispersions with essentially equivalent ease or difficulty because both contain terms quadratic in frequency [compare Eqs. (4) and (7)]. To elucidate the relative importances of the two mechanisms, Civan and Shporer,<sup>37</sup> and Fung<sup>62</sup> observed the  $^1\text{H}$   $T_1$ 's at 4.3, 8.1, and 35 MHz of muscle and brain tissue bathed in various concentrations of deuterated water ( $^2\text{H}_2\text{O}$ ) in Krebs or Ringers solution for 1–3 h. Since the gyromagnetic ratio of  $^2\text{H}$  is 0.15 that of  $^1\text{H}$ , the substitution of  $^2\text{H}_2\text{O}$  for  $^1\text{H}_2\text{O}$  in bulk water reduces the strength of intermolecular  $\text{H}_2\text{O}$ – $\text{H}_2\text{O}$  dipolar interactions for  $^1\text{H}$ . It also reduces the intramolecular H–H dipolar interaction since  $^1\text{H}_2\text{O}$  and  $^2\text{H}_2\text{O}$  undergo rampant chemical exchange to  $^1\text{HO}^2\text{H}$ . Thus, bulk water  $T_1$  rapidly increases as the ratio  $[^2\text{H}_2\text{O}/^1\text{H}_2\text{O}]$  increases. In tissue, the increase is much less: about 20% extrapolating to complete substitution compared to a factor of 24 for bulk water. Rustgi *et al.*<sup>140</sup> extended these measurements over the frequency range 15–60 MHz for muscle tissue, recording essentially the same observation.

This somewhat surprising and significant result is interpreted as evidence that tissue  $^1\text{H}$  relaxation is dominated by intermolecular interactions between macromolecules and water molecules in the first hydration layer. This is the only remaining relaxation mechanism that is transparent to the  $^2\text{H}_2\text{O}$  substitution.<sup>62</sup> The small 20% change observed is possibly attributable to chemical exchange between macromolecular and water hydrogens. The implication is that tissue  $T_1$  relaxation entirely hinges on the interaction between macromolecules and a single adsorbed layer of water. The relaxation mechanism may be either translational or rotational and likely involves the stronger H–H interactions. To explain the dispersion data, a distribution of correlation times in the neighborhood  $\sim 10 \text{ ns}$  is necessary. If the interaction is principally translational, as in the Escanye *et al.* model, then the residence time  $\tau_e$  also cannot be much longer than 10 ns.

## B. Spin-spin relaxation

An expression for the  $T_2$  dispersion corresponding to Eq. (3) is

$$\frac{1}{T_2} = \frac{3}{4} \gamma^4 \hbar^2 \left[ \frac{3}{8} J^0(0) + \frac{15}{4} J^1(\nu) + \frac{3}{8} J^2(2\nu) \right], \quad (9)$$

where  $J^0(0)$  is the static component of the spectral density functions<sup>1</sup> and includes here effects due to microscopic and molecular level field heterogeneity in biological tissue. Thus  $T_2$  is independent of frequency if the latter two terms in Eq. (9) are small compared to the first, static contribution. The similarity of structure of these terms with Eq. (3) ensures the frequency independence of  $T_2$  if  $T_2$  is much less than  $T_1$ . This is true of virtually all of the (nonfluid) tissues, except perhaps for the longest of the liquidlike ( $L$ ) multiple components of  $T_2$ , and for adipose whose  $T_1$  dispersion is essentially constant above 10 MHz anyway. The dispersions of long  $T_2$  components are more likely to follow those of the corresponding  $T_1$ 's. Like  $T_1$ ,  $T_2$  can also be equated to a sum of contributions from free and bound components in an expression analogous to Eq. (5). The static intramolecular spectral

density function due to rotation is  $J^0(0) = 6J^1(0)$  in Eq. (4), and the static intermolecular spectral density function, due to isotropic translational diffusion, is

$$J^0(0) = 2N/15dD = 2\pi N\eta/5kT$$

where  $\eta$  is the viscosity and  $k$  is Boltzmann's constant.<sup>1</sup>

Evidence for multicomponent relaxation times is less compelling for  $T_1$  than for  $T_2$ . The sparse multicomponent  $T_1$  data reported are largely explicable by sample or chemical heterogeneity. For example, in adipose tissues,  $^1\text{H}$  chemical shift spectroscopy reveals two principal components associated with  $\text{H}_2\text{O}$  and  $-\text{CH}_2-$  (macromolecular) hydrogens<sup>23</sup> with different  $T_1$  and  $T_2$  relaxation times thus far neglected in the above analysis. Breast and other tissues with large fatty components, high blood content, or other heterogeneity such as grey and white brain matter, or kidney cortex and medulla can easily yield multicomponent relaxation values. Multicomponent  $T_2$ 's that are not attributable to macroscopic or microscopic heterogeneity are difficult to explain at a molecular level. Given the similarity of mechanisms responsible for  $T_1$  and  $T_2$  relaxation, can multicomponent  $T_2$ 's coexist with single-valued  $T_1$ 's?

Hazlewood, Chang, and colleagues interpreted the multicomponent  $T_2$  data as evidence against the fast exchange model.<sup>34,75</sup> However, slow exchange would require residence times  $\tau_e$  of the order  $T_2$  ( $\sim 10$  ms), which could be expected to generate observable multicomponent  $T_1$  data. Diegel and Pintar responded that the different behavior is explicable via the static  $T_2$  spectral density term.<sup>47</sup> They observed dual component tissue  $T_{1\rho}$ 's (effectively, the  $T_1$  at extremely low frequency) from  $\sim 0$ –60 kHz equivalent to the  $T_2$  values and attributed to intercellular (150 ms) and intracellular (53 ms) water. The faster low-frequency  $1/T_{1\rho}$  and  $1/T_2$  relaxation rates can be accounted for by a  $\sim 10$   $\mu\text{s}$  correlation time identified with the residence time  $\tau_e$  for diffusion of water in the hydration layer.<sup>47,98</sup> This exchange diffusion is too slow to directly effect  $T_1$  relaxation between 1–100 MHz, but, since  $\tau_e \ll T_1$ , it strongly averages the different  $T_1$  values from the various compartments leaving the observed  $T_1$  single valued in the  $> 1$  ms range.  $T_{1\rho}$  measurements in normal and deuterated muscle, spleen, and kidney by Rustgi *et al.*<sup>140</sup> confirm the importance of exchange diffusion as a relaxation process at extremely low frequencies. The exchange diffusion can directly effect tissue water  $T_2$ 's by exposing water molecules to static field inhomogeneities at the exchange interface: Fung and McGaughy<sup>64</sup> note microscopic field inhomogeneity as a likely explanation why  $T_2 < T_1$  in tissue.

This model is incompatible with the Escanye *et al.* view of  $T_1$  dispersions in the 1–100 MHz range dominated by diffusion, since it would require  $\tau_e \sim \tau_d$ , but is compatible with the rotational modeling of  $T_1$ . The free water correlation time is still  $\sim 1$  ps, much faster than both the exchange correlation time  $\tau_e \sim 10$   $\mu\text{s}$  and the suggested distribution of rotational correlation times  $\tau$  in the range 10 ns responsible for  $T_1$  relaxation.

Some additional information on multicomponent  $T_2$ 's is provided by Peemoeller *et al.*<sup>128</sup> who analyzed the relative contributions of water and macromolecular hydrogens to

each component in mouse muscle by comparison with tissue soaked in an osmotically balanced  $^2\text{H}_2\text{O}$  solution for 4 h. They ascribe a 143 ms ( $L$ ) and a 24  $\mu\text{s}$  ( $S$ )  $T_2$  component to macromolecules, a 40 ms ( $SL$ ) component to water alone, and a 5 ms ( $SS$ ) component to both water (70%) and macromolecules (30%). This is a more likely allocation of  $T_2$  components than the Diegel and Pintar intercellular/intracellular assignment,<sup>47</sup> and is consistent with the aforementioned observation of discrete  $\text{H}_2\text{O}$  and  $-\text{CH}_2-$  peaks in some tissue  $^1\text{H}$  NMR spectra.<sup>23</sup> Aside from the possibility of chemical exchange, macromolecular components cannot be expected to participate in fast exchange.

### C. Temperature dependence

The relaxation times depend on temperature via the rotational and translational correlation times  $\tau_i$  and  $\tau_d$ . Setting

$$\tau_i = \tau_{i0} \exp(E_{ia}/kT) \quad (10)$$

for the bound water hydrogens in Eqs. (3)–(7) and (9), where  $\tau_{i0}$  and  $E_{ia}$  are, respectively, a constant and the activation energy for the  $i$ th mode of motion,<sup>1</sup> could precisely define the temperature dependence of the relaxation times if indeed the relaxation time model were precisely understood. Assuming the bound fraction  $b$  is temperature independent, then in the limit  $2\pi\nu\tau_i \ll 1$  the frequency-dependent denominators of the rotational spectral density functions [Eq. (4)] approach unity, and substitution of Eq. (10) in Eqs. (5) and (3) gives

$$T_{1f} \sim \exp(-E_{af}/kT) \text{ and } T_{1b} \sim \exp(-E_{ab}/kT), \quad (11)$$

or more crudely,

$$T_1 \sim \exp(-E_a/kT),$$

where  $E_{af}$ ,  $E_{ab}$ , and  $E_a$  are activation energies for the  $T_{1f}$ ,  $T_{1b}$ , and  $T_1$  processes. This dependence is assumed by Lewa and Majewska<sup>102</sup> and Parker *et al.*<sup>125</sup> to explain their observed linear behavior of  $T_1$  with temperature. It should also describe the  $T_2$  temperature dependence when the static spectral density term is dominant. For small temperature variations, the series expansion for exponentials suggests an approximately linear relationship between  $T_1$  and  $1/T$ , with  $T_1$  increasing with increasing temperature. Furthermore, if the reorientation is random, then Stokes' formula  $D_r = kT/8\pi a\eta$  for the rotational diffusion coefficient of spheres, where  $a$  equals the molecular radius, provides  $\tau_i = 4\pi\eta a^3/3kT$ , instead of Eq. (10). Thus the same result  $T_1 \propto 1/T$  obtains directly.<sup>1,19</sup> In models dominated by translational diffusion, application of Stokes' formula  $D = kT/3\pi d\mu$  (so  $\tau_d = 3\pi d^3\eta/2kT$ ) for the translational diffusion coefficient to Eqs. (7) and (3) repeats this result.<sup>1,19</sup> Since absolute temperature changes relatively little between 0 and 40  $^\circ\text{C}$ ,  $T_1$  also varies roughly linearly with  $T$ . Extending the temperature range beyond this risks irreversible structural transitions in tissue not representative of the physiological state.<sup>102</sup>

The small temperature range and the relatively modest variations in the observed  $T_1$ 's so induced, are likely responsible for the success of these simple formulations for the temperature dependence, despite the somewhat dubious assumptions. Moreover, to explain the experimental tissue  $T_1$  dispersions requires  $2\pi\nu\tau_i \gtrsim 1$  for the dominant relaxation processes<sup>54</sup> in models employing Eqs. (4) or (7), thereby



modifying the above proportionalities and introducing frequency dependence to the temperature dependence. Indeed, under this condition, the denominators of Eqs. (4) and (7) predominate, and application of either Stokes' formulas or Eq. (10) anticipates a decreasing  $T_1$  with increasing temperature, contrary to the data. The dilemma is resolved in the  $T_1$  model employing a log-Gaussian distribution of correlation times by incorporating temperature dependence into the distribution function parameters [Eq. (6)] via  $\alpha = \alpha_0 \sqrt{T}$ , and

$$\tau_0 = \tau_{0\infty} \exp(E_a/kT),$$

where  $\alpha_0$  and  $\tau_{0\infty}$  are constants.<sup>63,64</sup> Fung and colleague's simultaneous fitting of muscle and liver  $T_1$  dispersion data from 4.5 to 60 MHz over -70 to 40 °C utilizing this model is persuasive evidence for its validity.

The observed increase in the derivative of  $T_1$  with respect to temperature ( $\partial T_1/\partial T$ ) with increasing frequency is an important feature of the data, consistent with the distributed correlation times of Fung *et al.*'s model. In fact, since the temperature-dependent correlation times appear as coefficients of the frequency dependent terms in Eqs. (4) and (7), Eq. (1) might suggest  $\partial T_1/\partial T \sim \nu^B$  with  $B \sim 1/3$ . Thus an eightfold frequency change from 7.5 to 60 MHz could result in an approximately twofold increase in the temperature dependence, in fair agreement with Fung *et al.*'s observation on mouse muscle and liver,<sup>62</sup> and the 20-fold increase in frequency between 1–20 MHz studied by Koenig *et al.* might account for a threefold increase in temperature dependence in approximate agreement with their rabbit blood data.<sup>99</sup> However, above 20 MHz the magnitude of the difference between  $T_1$  values measured at room temperature and at physiological temperature is unresolved due to the dearth of physiological temperature data from all tissues except Fung *et al.*'s muscle and liver data. If the larger temperature dependences noted by Fung *et al.* were generally applicable, then the tissue curves (Figs. 1–9) could seriously underestimate the high-frequency behavior of the *in vivo*  $T_1$  values. Below 20 MHz, the consensus from the tables and *in vivo* versus *in vitro* plot (Fig. 12) is that temperature differences between 20 and 37 °C do not significantly affect the  $T_1$  values of nonfluid tissues.

The slight increase in  $T_2$  with decreasing temperature observed by Belton *et al.*<sup>14</sup> is consistent with the role of the exchange process as a  $T_2$  relaxation mechanism,<sup>14,47</sup> transparent to  $T_1$  processes except for the mixing of free and bound values. As the temperature decreases, exchange slows and contributes less to  $T_2$  relaxation so that  $T_2$  initially increases.<sup>14</sup> Eventually  $T_2$  decreases as other molecular motions slow with further declines in temperature. No frequency variations in tissue  $T_2$  temperature dependence over 1–100 MHz are anticipated in view of the apparent frequency independence of  $T_2$ .

#### D. Tissue, species, and age dependence

The  $^1\text{H}$  tissue water relaxation times measure molecular level structure and motion and therefore depend on the organization and composition of the tissue. Investigations of the correlation between  $T_1$  and tissue water content are legion.<sup>6,26,36,43,46,61,76,80,86,87,92–94,96,104,108,127,130,133,134,142,144</sup>

The mean fractional water contents by weight of normal rat and mouse liver, kidney, spleen, muscle, brain, and adipose tissue are  $0.69 \pm 0.01$ ,  $0.74 \pm 0.01$ ,  $0.77 \pm 0.02$ ,  $0.75 \pm 0.02$ ,  $0.79 \pm 0.01$ ,  $0.18 \pm 0.03$ , respectively, averaged from Refs. 26, 43, 46, 76, 80, 86, 87, 92, 96, 97, 130, 134, 142, and 144. These correlate directly with  $T_1$ : the higher the water content, the longer the  $T_1$ , prompting Mansfield and Morris<sup>111</sup> to write for a (nonadipose) tissue with fractional water content  $w$

$$T_1 = 7.94 w - 5.16, \quad (12)$$

assuming Kiricuta *et al.*'s 60-MHz rat data.<sup>96</sup> This relation emphasizes the observation that quite marginal changes in  $w$  are associated with large variations in  $T_1$ . In fact, the changes in  $w$  with respect to  $T_1$  are so marginal that the physical significance of the correlation between  $T_1$  and water content alone is doubtful.<sup>108,133</sup> Differences in macromolecular composition and structure, which could well influence the amount and motion of adsorbed water molecules and indeed the total tissue water content, thus probably constitute the primary source of variations in  $T_1$  amongst different tissue types.

A remarkable feature of the relaxation data is its apparent independence of species. From the NMR standpoint, a human muscle is a rat muscle is a pig muscle is a frog muscle is a chicken muscle, etc., notwithstanding potential variations due to temperature. Again composition and structure are possible causes. Mansfield and Morris<sup>111</sup> tabulate human tissue water contents that are 2% to 7% higher than the rat/mouse averages cited above. In view of Eq. (12), these differences are too significant to permit the species independence of relaxation times, suggesting that water content is not directly responsible for the species' similarities amongst relaxation times. Macromolecular composition and structure are important to tissue function as well as to the relaxation times. Thus once the function has evolved, differences amongst species are apparently only of secondary importance at the molecular NMR level. Alternatively, it is possible that the differences in water content cited reflect systematic differences in the methods of measurement of water content.

Mansfield and Morris<sup>111</sup> also note a 2.5% per decade decline in human body water content from ages 40 to 70, which should dramatically reduce the corresponding  $T_1$ 's if Eq. (12) were a determining influence. Subject age is a widely neglected parameter in human studies that could potentially create chaos of efforts to develop normal ranges of  $T_1$ , should significant variations occur. For immature tissue, large elevations in  $T_1$  (Fig. 13) do correlate with increased water content, yet the possible role of macromolecular structural development as the principal determining factor again cannot be ruled out.

#### V. ERROR AND OMISSIONS

While evidence for the dependence of tissue relaxation times on temperature, time after excision, *in vivo* versus *in vitro* status, time of day, age, and species exists, these factors are demonstrably not entirely responsible for the scatter amongst  $T_1$  and  $T_2$  tissue dispersions. Other possible factors

are inherent tissue heterogeneity, sample handling techniques, the NMR measurement methods, the existence of multiple  $T_2$  components, as well as presently unidentified sources. Tissue heterogeneity is unlikely to significantly influence scatter because of the large number of samples typically studied and the relatively small standard deviations quoted for individual  $T_1$  points. Sample handling is a key issue for *in vitro* studies, addressed in depth by Beall.<sup>8</sup> We recommend that investigators perform measurements as soon as possible after death and excision, and that measurements for *in vivo* comparison be performed at physiological temperatures with samples that have not been overheated, frozen, homogenized, soaked, dehydrated, or otherwise abused.

The reviewed *in vitro*  $T_1$  measurements were performed by either inversion recovery, or by partial saturation, or saturation recovery, or in one case by rapid ramping of the field,<sup>99</sup> or by the less accurate null method. The few investigators that employed the null technique almost invariably verify experimental accuracy by comparison with measurements obtained by the other methods. *In vitro*  $T_2$  measurements were performed mainly by the standard Carr-Purcell or Carr-Purcell-Meiboom-Gill methods. Therefore, we could not objectively discriminate against  $T_1$  and  $T_2$  data on the basis of measurement technique, nor were there sufficient grounds to exclude data due to sample handling transgressions, except where stated in the Sec. II.

Perhaps the most dubious practices abound in the measurement of relaxation times, particularly  $T_2$ , *in vivo* utilizing NMR imaging techniques. To expedite patient scan times,  $T_1$  and  $T_2$  measurements are typically performed using only two points on the nuclear magnetization relaxation curves for each image picture element.<sup>32,33,44,45,49,70,79,82,83,88,109,110,116,117,139,148-152,158</sup> Unfortunately, the standard expressions employed for computing  $T_1$  from inversion or saturation recovery presume precise 90° or 180° radiofrequency (rf) NMR pulses at each picture point across the image plane,<sup>51</sup> a difficult task for conventional NMR transmitter coil designs. The effect is dramatically illustrated by Gore *et al.*,<sup>70</sup> who reported  $T_1$  variations of up to 60% from the same sample as a result of increasing the relaxation recovery time  $t$  from 0.2 to 0.4 s. They attributed the variations to multiple-component  $T_1$  behavior which our review deems unlikely. A prudent approach to accurate  $T_1$  measurement in the presence of inhomogeneous rf fields in NMR imaging is to use a three-parameter fit to the signal intensity

$$S = P + Q \exp(-t/T_1), \quad (13)$$

where  $P$ ,  $Q$ , and  $T_1$  are fitting constants.<sup>56</sup> Obviously, more than two data points would be required.

The situation is worse for *in vivo*  $T_2$  studies since multiple components are widely identified *in vitro*. Hence, Gore *et al.*<sup>70</sup> tabulated variations in  $T_2$  of up to 350% comparing values from the same sample computed from spin echoes occurring at 32 and 64 ms after the initial 90° rf pulse. Furthermore, the pulsed gradient spin-echo imaging experiment employed in  $T_2$  imaging studies is a facsimile of the standard Stejskal and Tanner pulsed gradient diffusion measurement technique.<sup>153</sup> Since bulk tissue diffusion coefficients are sig-

nificant fractions of pure water values,<sup>74,75</sup> attenuation of computed  $T_2$ 's by diffusion effects is quite predictable. Diffusion and ignorance of multiple components may thus substantially account for the sad state of the  $T_2$  data. If dual-point  $T_1$  and  $T_2$  imaging measurements become convention, and if the resultant  $T_1$  and  $T_2$  values are to be useful as diagnostic parameters independent of the particular imaging system and suitable for comparison, then standardized image sequence timing parameters should be adopted and any rf inhomogeneity problems solved.

The sparsity of relaxation data above 30 MHz and the absence of *in vivo* data above 15 MHz are additional deficiencies, although we certainly do not claim to have found all of the published measurements.

## VI. CONCLUSIONS

The principal determinants of  $T_1$  relaxation in normal biological tissue in the range 1–100 MHz are NMR frequency ( $\nu$ ) and tissue type. All of the tissue  $T_1$  dispersions studied obey the simple relationship  $T_1 = A\nu^B$ , where  $A$  and  $B$  are parameters dependent on tissue type and  $B \sim 1/3$ . This expression gives an equivalent or better fit to  $T_1$  data than previously used expressions and models and is simple enough to enable rapid computation of  $T_1$  values at any desired frequency between 1 and 100 MHz. The standard deviations of  $T_1$  from the fitted curves are about 20% reflecting mainly systematic errors not readily identifiable with species, temperature, *in vivo* versus *in vitro* status, time after excision, or age differences. Fetal and immature tissue excluded from this analysis exhibit dramatically elevated  $T_1$  values. Most data are recorded at room temperature or physiological temperature, but there is a dearth of the latter measurements above 20 MHz. Evidence that the temperature dependence of  $T_1$  increases significantly at higher frequencies could, therefore, result in our mean curves underestimating the high-frequency physiological temperature data. Virtually all researchers report single component  $T_1$  values. However, breast tissue  $T_1$  dispersions can be resolved into two components comprising adipose and fibrous tissue which have essentially equivalent dispersions to those of skeletal muscle and adipose. Dual components can arise from macroscopic tissue heterogeneity or from the discrete chemical species  $H_2O$  and  $-CH_2-$  on macromolecules when these are sufficiently mobile to be detectable on the time scale of the NMR experiment.

The principal determinant of  $T_2$  relaxation in normal biological tissue in the range 1–100 MHz is tissue type. No substantial dependence on NMR frequency, temperature, *in vivo* versus *in vitro* status, time after excision, or age can be differentiated within systematic errors of about 30%. Therefore average  $T_2$  values are tabulated as constants for each tissue. Substantial evidence for multiple  $T_2$  components exists. In muscle, the major component ( $T_2 \sim 40$  ms), constituting about 75% of the signal, derives from tissue water. There exist very long ( $T_2 \sim 140$  ms) and very short ( $T_2 \sim 20$   $\mu$ s)  $T_2$  components from macromolecules contributing about 7% and 11% each, and a short  $T_2$  component ( $T_2 \sim 5$  ms) of about 7% derived from both water and macromolecules. Multicomponent  $T_2$ 's and diffusion in the presence of imag-



ing gradients are deleterious factors affecting *in vivo*  $T_2$  measurements which must be dealt with.

The observed tissue  $T_1$  and  $T_2$  relaxation data can be substantially accounted for by the FETS model with free and bound phases of water undergoing rapid exchange. There is disagreement concerning the detailed mechanisms responsible for relaxation, however we tentatively offer the following scenario consistent with the reviewed data and which incorporates elements from the models of Fung *et al.*, Diegel and Pintar, Rustgi *et al.*, and the results of the deuterated water exchange experiments of Fung, Rustgi *et al.*, Civan and Shporer, and Peemoeller *et al.*

Water in the free phase undergoes rapid, probably correlated, rotational and translational motion with a correlation time of order 1 ps. This is too fast to directly affect relaxation between 1 and 100 MHz so the  $T_1$  of the free phase is long ( $T_{1f} \sim 1.7$  s) like ordinary water and independent of frequency. In muscle, the bound phase constitutes about 10% of the total tissue water content and consists of a single hydration layer adsorbed on the surface of macromolecules. The intramolecular rotational correlation time of these water molecules is probably still about 1 ps, but faster relaxation of water hydrogen is facilitated via intermolecular interactions involving mainly macromolecular hydrogen. The latter mechanisms requires a log-Gaussian or similar distribution of correlation times for motion, probably rotational, in the NMR frequency range, of order 10 ns. This faster intermolecular relaxation process is primarily responsible for the observed  $T_1$  frequency, temperature, tissue type, and age dependencies. The bound water undergoes exchange diffusion with the free component with a slower correlation time of about 10  $\mu$ s, which may be identified as the residence time in the bound state. The exchange diffusion correlation time is too long to facilitate  $T_1$  relaxation directly but could provide an important relaxation mechanism for  $T_{1p}$  and  $T_2$ . Nevertheless, it is sufficiently short to prohibit resolution of the free and bound water  $T_1$ 's on the time scale of the  $T_1$  experiment. Thus the observed water  $T_1$  relaxation rate ( $1/T_1$ ) is essentially equal to the sum of the free and bound water relaxation rates.

Unlike  $T_1$ ,  $T_2$  largely measures the low-frequency and static components of molecular motion and can therefore discriminate free and bound water and macromolecule phases. The bound water and the corresponding macromolecular adsorption surface must share the same low-frequency or static motional environment and can therefore be assigned the joint short  $T_2$  component of about 5 ms in muscle. The major free water component exhibits a unique, significantly longer  $T_2$  value ( $\sim 40$  ms in muscle) reflecting its greater mobility. However the free water component  $T_2$  value is much less than the free water  $T_1$  values ( $\sim 500$  ms) owing to an exchange diffusion relaxation mechanism. Thus, the free water component  $T_2$  relaxation rate ( $1/T_2$ ) is equal to the sum of the rate due to exchange diffusion at the exchange interface, and the much slower rate in the true liquid water phase. The exchange diffusion rate decreases with decreasing temperature, causing the free water component  $T_2$  to increase slightly. Since this is the major component, and  $T_2$  varies with tissue type, the exchange diffusion correlation

time is likely tissue dependent. A physical candidate for the exchange diffusion relaxation mechanism is local static field gradients between the exchange interface and the free phase due to the presence of the macromolecules. The remaining two macromolecular  $T_2$  components have no water counterparts. The extremely short component around 20  $\mu$ s probably corresponds to rigid membrane or protein structures not normally observable in the NMR experiment, and the very long 140-ms component to highly mobile hydrogen on fatty acids, with essentially no hydration layer. The dominant role of low-frequency relaxation mechanisms for all  $T_2$  components except the very long component ensures  $T_2$  dispersions independent of the NMR frequency. The 140-ms fatty acid  $T_2$  component may be associated with the comparably valued  $T_1$  observed in adipose tissue, in which case its frequency dispersion will be similar.

Further effort is necessary to evaluate the full range of fitting parameters for the model peculiar to each tissue, and to tighten the uncertainty of the normal  $T_1$  and  $T_2$  values. It is imperative that guidelines be established for reproducible measurement of tissue NMR relaxation *in vivo*.

*Note added in proof:* Koenig *et al.*<sup>162</sup> recently published  $^1\text{H}$   $T_1$  dispersions of normal and partially deuterated rat tissue from 10 kHz to 100 MHz. The Fung and Rustgi *et al.* observations on deuterated tissues are confirmed over 1–100 MHz. Koenig *et al.* attribute the 1–100 MHz dispersions to intermolecular interactions at the macromolecule–water interface. Below 1 MHz the difference between the normal and partially deuterated tissue  $T_1$  increased to twofold at 10 kHz, indicating the increasing role of intra- (and possibly inter-) molecular  $\text{H}_2\text{O}$ – $\text{H}_2\text{O}$  interactions at low frequencies. These observations are consistent with our best-guess model. Slight structure ( $\sim 6\%$   $T_1$ ) was observed in the heart muscle dispersions between 2 and 3 MHz and attributed to magnetization transfer (cross relaxation) between  $\text{H}_2\text{O}$  and  $^{14}\text{N}$  nuclei on protein amides. A similar effect is noted in leeches by Kim-mich *et al.*<sup>163</sup>

Bakker and Vriend<sup>164</sup> published statistically significant dual-component excised mice fat, kidney, muscle, and spleen tissue  $^1\text{H}$   $T_1$ 's at 60 MHz. Except for fat, results showed a short component of 2–10 ms constituting 5%–8% of the magnetization, and a long component of comparable value of those cited herein. Dual components are attributed to the use of long (150  $\mu$ s)  $180^\circ$  rf pulses in an inversion recovery sequence combined with a mechanism of  $^1\text{H}$ – $^1\text{H}$  cross relaxation<sup>165</sup> between  $\text{H}_2\text{O}$  and macromolecules at the interface.

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